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COGNITIVE FUNCTION IN CHRONIC NON-MALIGNANT PAIN PATIENTS TREATED WITH SUSTAINED-RELEASE MORPHINE SULFATE (AVINZA)

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Dedication

This work is dedicated to all those who suffer with pain.

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COGNITIVE FUNCTION IN CHRONIC NON-MALIGNANT PAIN PATIENTS TREATED WITH SUSTAINED-RELEASE MORPHINE SULFATE (AVINZA)

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The purpose of this study is to evaluate the association between sustained-release morphine (Avinza®), and performance on neuropsychological tests assessing short-term memory, information processing, and motor skills in chronic pain patients, while controlling for stages of pain model variables and the effects of benzodiazepines. A convenience sampling procedure was utilized to enroll a sample of patients who had a trial of short-acting narcotic analgesics for their chronic non-malignant pain. Enrolled patients were treated with long-acting morphine Avinza.® Patient interviews were conducted at enrollment and one-month follow-up. A total of 129 patients were enrolled in the study. Mean pain intensity ratings at the highest, lowest, and average levels in the previous week were lower at follow-up (10.90, 4.56. 7.64) than at baseline (12.71, 6.76, 10.01) respectively. Reduction in pain levels was associated

with a corresponding reduction in levels of pain unpleasantness, pain suffering, and pain behaviors. The models evaluating the associations between the stages of pain model variables, morphine dose, benzodiazepine dose, and digit span test (chi square = 147.79, p = 0.76), digit symbol test (chi square = 128.06, p = 0.5), and paced auditory serial attention test fit the data well (chi square = 160.39, p = 0.85). There was a statistically significant inverse association between frequency of pain behaviors and digit span test scores at baseline (-0.49, p = 0.01). Although the association between pain behaviors and digit symbol test scores (- 17. 0 %, p = 0.09) and paced auditory serial addition test scores (-4.0%, p = .28) at baseline were not statistically significant, a large negative effect was found. At follow-up, the association between pain behaviors and digit span test was positive and not significant. The negative association between frequency of pain behaviors and digit symbol test scores (-4.4%, p = 0.67) and paced auditory serial addition test scores (-2.8%, p = 0.21) at follow-up were considerably weaker. There were no significant association between opioid dose and cognitive function test scores. Opioid therapy, particularly, sustained-release morphine therapy (Avinza) does not contribute to cognitive impairment in chronic pain patients.

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Chapter 1: Background and Introduction

1.1 Introduction

The number of people in the United States that suffer from pain is estimated to be in the range of 35 to 75 million.[1] Numerous therapeutic and non-therapeutic strategies have been applied in the management of pain. Narcotic analgesics (opioids) are often utilized in chronic pain as a last resort when all other pharmaco-therapeutic options have failed.

The use of opioids in the treatment of chronic non-malignant pain (CNMP) is not without debate or controversy. There is a lack of conclusive evidence regarding the risks and benefits of opioid therapy in the management of CNMP.[2] Results from a study about physician attitudes towards use of opioids in CNMP showed that 42 percent, 57 percent, and 75 percent of respondents would never prescribe long acting schedule II opioids to patients with post herpetic neuralgia, chronic low back pain, and chronic daily headache, respectively.[3] Cognitive impairment due to opioids is often cited as a cause for concern; this study outlines a proposal to examine the issue further.

A number of studies have found that pain, in addition to opioid use is associated with cognitive dysfunction.[4,5,6,7,8] This study questions whether pain

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[1] Walsh NE et al. Cited by: Wade JB, Hart RP. Attention and the stages of pain processing. *Pain Medicine*. 2002;3:30-38.
[2] Potter M, Schafer S, Gonzalez-Mendez E, et al. Opioids for chronic non malignant pain. *Journal of Family Practice*. 2001;50:145-159.
[3] Ibid.
[4] Hart RP, Martelli MF, Zasler ND. Chronic pain and neuropsychological functioning. *Neuropsychology Review*. 2000;10:131-149.
[5] Schwartz DP, Barth JT, Dane JR, Drenan SE, DeGood DE, Rowlingson JC. Cognitive deficits in chronic pain patients with and without a history of head/neck injury: development of a brief screening battery. *Clinical Journal of Pain*. 1987;3:94-101.
[6] Dufton BD. Cognitive failure and chronic pain. *International Journal of Psychiatry in Medicine.* 1989;19:291-297.
[7] Eccleston C. Chronic pain and distraction: An experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behavior Research and Therapy*. 1995;33:391-405.
[8] Eccleston C, Crombez G, Aldrich S, Stannard C. Attention and somatic awareness in chronic pain. *Pain*. 1997;72:209-215.

control with long-acting morphine, particularly Avinza® is associated with an improvement in cognitive symptoms. "Studies examining opioid-related cognitive dysfunction in chronic non-malignant pain are limited, and overall they provide a conflicting series of results. Regarding the choice among stronger opioids, there is little evidence to suggest that one opioid is superior to any other regarding cognitive side effects with the exception of meperidine and perhaps methadone."[9] A review of five controlled studies in the treatment of chronic pain with opioid analgesics showed inconsistent results on outcome variables such as "disability," "emotional distress," "quality of life," and "psychological or functional impairment."[10]

1.2 Purpose of the Study

Opioid use on a chronic basis may be associated with some cognitive impairment. There are very few studies that have examined the effects of opioid use on cognitive impairment in chronic pain patients. Furthermore, only one study has examined this association for long-acting narcotic analgesics. None of these studies have utilized a theoretical framework to address this complex issue. The purpose of this study is to utilize the stages of pain model to assess cognitive function in chronic non-malignant pain patients who are stabilized on long acting narcotic analgesic therapy.

[9] Lawlor PG. The panorama of opioid-related cognitive dysfunction in patients with cancer. *Cancer*. 2002: 94:1836-1853.
[10] Dickinson BD, Altman RD, Nielsen NH, Williams MA. Use of opioids to treat chronic, noncancer pain. *The Western Journal of Medicine*. 2000;172:107-115.

1.3 Literature Review

1.3.1 Definition of Chronic Pain

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, or both.[11] Pain that persists for a period of three months is often referred to as being chronic.[12] Additionally, pain that remains untreated or uncontrolled beyond an anticipated duration may also qualify as persistent pain.[13] Chronic pain has been characterized as an illness rather than a disease and it encompasses physical discomfort, psychological suffering, activity limitation, and psychosocial difficulties.[14]

A consensus statement issued by the the *American Academy of Pain Medicine* (AAPM) and the *American Pain Society* (APS) states that there are no nationally accepted clinical practice guidelines for the management of CNMP. Despite the availability of various therapeutic, surgical, and behavioral interventions for the management of non-cancer pain, the condition is often left untreated or under treated. Inadequate treatment contributes to excessive utilization of health services, reduced productivity, and poor quality of life (QOL).[15]

1.3.2 Epidemiology and Economics of Chronic Non-malignant Pain (CNMP)

According to a World Health Organization (WHO) survey, 22 percent (1196/5438) of patients sampled reported experiencing persistent pain defined as pain

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[11] Merskey H, Bogduk N, eds. Classification of chronic pain: Descriptions of chronic pain syndromes and definitions of chronic pain syndromes and definitions of pain terms. 2nd ed. Seattle, WA: IASP Press; 1993:3-4.
[12] Andersson GBJ. Epidemiological features of chronic low back pain. *Lancet.* 1999;354:581-585.
[13] Weitz MA, Burke SM. Persistent pain in long term care: overcoming barriers to improve resident care. *The Consultant Pharmacist*. 2002;17(SupplB):3-9.
[14] Turk DC, Monarch ES. Biopsychosocial perspective on chronic pain. In: Turk DC, Gatchel RJ, eds. *Psychological approaches to pain management*. New York, NY:The Guilford Press;2002.
[15] American Pain Society. The Use of opioids for the treatment of chronic pain. A consensus statement from American Academy of Pain Medicine and American Pain Society. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed on Feb 22, 2003.

that persisted for six or more months in a year.[16] Back pain, headache, and joint pain were reported to occur most frequently. Participants also indicated that pain interfered with numerous activities and was associated with depression. Results from a follow-up study showed that 49.2 percent of these patients continued to meet the criteria for persistent pain. Pain at two or more sites, depressed mood, and age (greater than 40) were factors predictive of a poor outcome.[17] In a review of several international studies, Maniadakis and Gray reported that the prevalence of back pain at any given time ranges from 12-35 percent in the population.[18] Approximately 30 percent of the population in industrialized nations experience chronic pain of some form at a given time, and nearly half of the sufferers experience partial or complete disability.[19] Back pain ranks second in the United States (US) as a reason for visits to the physician, and is the fifth leading cause of hospitalizations.[20]

A cost-of-illness study in the United Kingdom (UK) estimated the direct costs of back pain to be £1632 million, of which physiotherapy (37%) and utilization of hospital services (31%) accounted for majority of the costs.[21] In 1990, the direct costs of back pain were estimated to be $24.3 billion in the United States.[22]

In 1991, costs due to absenteeism and disability payments in the Netherlands were estimated at $US 4.6 billion and $US 1.5 billion.[23] The human capital approach and the friction cost method were used to estimate productivity losses. In 1998, indirect costs (time lost from work and caregiver time) to the UK health system due to back pain were estimated to be £ 5018 million.[24] In the United States,

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[16] Gureje O, Von Korpff M, Simon GE, Gater R. Persistent pain and well being: a World Health Organization study in primary care. *Journal of the American Medical Association.* 1998;280:146-151.
[17] Gureje O, Simon GE, Von Korpff M. A cross-national study of the course of persistent pain in primary care. *Pain*. 2001;92:195-200.
[18] Maniadakis N, Grey A. The economic burden of back pain in the UK. *Pain*. 2000;84:95-103.
[19] Loeser JD. Economic implications of pain management. *Acta Anaesthesiologica Scandinavica*. 1999;43:957-959.
[20] Andersson GBJ. Epidemiological features of chronic low back pain. *Lancet*. 1999;354:581-585.
[21] Ibid.
[22] Frymoyer JW, Cars Varil WL. Cited by: Hemmila HM. Quality of life and cost of care of back pain patient. *Spine.* 2002;27:647-653.
[23] Hutubessy RCW, Van Tulder MW, Vondeling H, Bouter LM. Indirect costs of pain in the Netherlands: a comparison of the human capital method with the friction cost method. *Pain*. 1999;80:201-207
[24] Maniadakis N, Grey A. The economic burden of back pain in the UK. *Pain*. 2000;84:95-103.

approximately 2 percent of injured workers receive disability payments each year due to chronic back pain.[25] Indirect costs in 1990 ranged from $75-100 billion.

Outcomes among many individuals with chronic pain do not improve even after diagnosis and treatment, indicating a poor understanding of the pathological causes of pain. Chronic pain is often under treated in both ambulatory and long-term care settings. Untreated pain can cause several undesirable effects such as anxiety, agitation, depression, cognitive dysfunction, and a variety of activity limitations.[26] Poor QOL and diminished functional ability are commonly observed among these individuals. It has been reported that back pain significantly limits activity in the younger population (less than 45 years).[27] Pain being a multidimensional experience adversely affects physical functioning, psychological functioning, and social functioning.[28]

The complex nature of pain and the difficulties associated in determining the causal factors that are associated with chronic pain limit the development and use of standardized treatment protocols and algorithms. In addition to causal factors and variations in treatment patterns, patient response to therapy and ultimate satisfaction with the treatment varies greatly from one patient to another. The need for cost-consciousness and the focus on consumer satisfaction in healthcare necessitate the measurement of health related quality of life (HRQOL) and other treatment related outcomes among patients suffering from chronic pain.

1.3.3 Chronic Pain Syndrome – Diagnostic Criteria

The following is a list of characteristics that can be used to identify a chronic pain syndrome (CPS) patient:

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[25] Andersson GBJ. Epidemiological features of chronic low back pain. *Lancet*. 1999;354:581-585.
[26] Weitz MA, Burke SM. Persistent pain in long term care: overcoming barriers to improve resident care. *The Consultant Pharmacist*. 2002;17SupplB:3-9.
[27] Loeser JD. Economic implications of pain management. *Acta Anaesthesiologica Scandinavica*. 1999;43:957-959.
[28] Marcus DA. Treatment of chronic nonmalignant pain. *American Family Physician*. 2000;61:1331-1440.

(a) reports of persistent (i.e., at least three months duration) pain, which may be consistent with or significantly out of proportion to physical findings;
(b) demonstrates or has demonstrated a progressive deterioration in ability to function at home, socially, and at work;
(c) shows or has shown a progressive increase in health care utilization (such as repeated physical evaluations, diagnostic tests, requests for pain medications, and/or invasive medical procedures);
(d) demonstrates mood disturbance; and
(e) exhibits clinically significant anger and hostility.[29]

According to this definition, any patient that presents with persistent pain, and two additional characteristics listed above may be categorized as a CPS patient. Patients with a history of excess utilization or deterioration in function that has stabilized in the recent past are also CPS candidates.

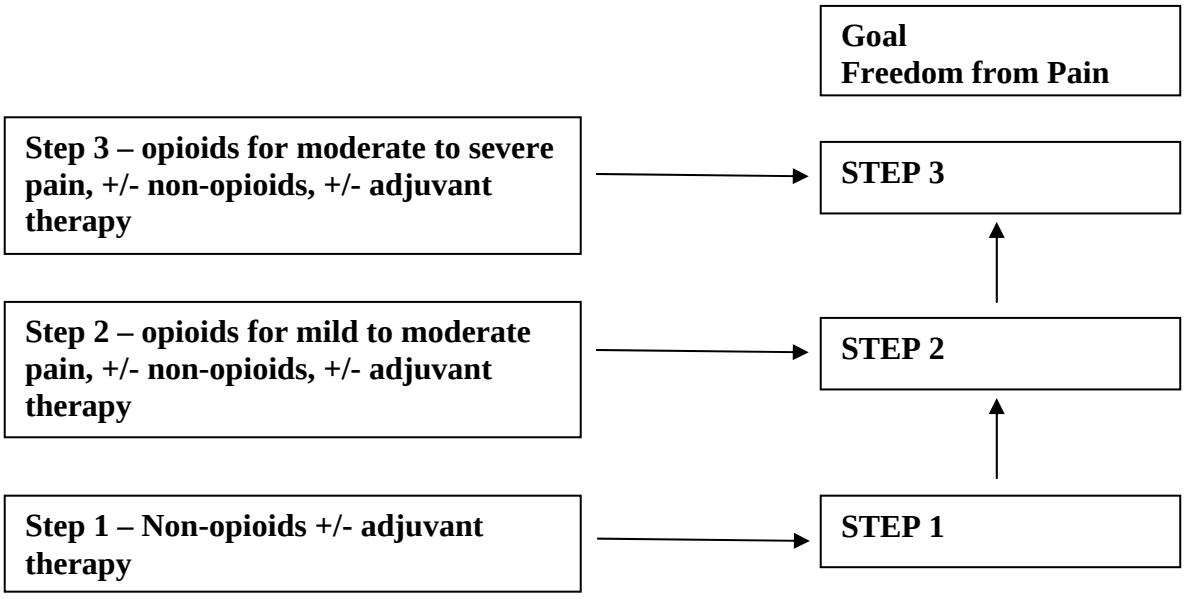
The appropriate management of any disease state is based on established algorithms that are primarily developed on the basis of observation in clinical practice, empirical evidence based on randomized trials and additional studies, and expert opinion. Evidence-based guidelines serve as a critical roadmap in making assessments and developing treatment strategies. Practice guidelines play an important role in standardizing the level of care patients receive and enable comparisons across different groups of patients. "Guidelines, which have been developed for opioid therapy in patients with chronic non-cancer pain, are based on empirical clinical judgment or consensus and have not been validated in large prospective clinical trials."[30]

[29] Sanders SH, Harden RN, Benson SE, Vicente PJ. Clinical practice guidelines for chronic non-malignant pain syndrome patients II: An evidence-based approach. *Journal of Back and Musculoskeletal Rehabilitation.* 1999;13:47-58.
[30] Nedeljkovik SS, Wasan A, Jamison RN. Assessment of efficacy of long-term opioid therapy in pain patients with substance abuse potential. *The Clinical Journal of Pain*. 2002;18:S39-S51.

1.3.4 Pain Management Guidelines

The World Health Organization's analgesic ladder has been widely accepted as a useful tool in the management of acute pain and cancer-related pain. In the absence of specific guidelines, this tool has also been widely utilized for the management of chronic non-malignant pain. The following figure is a representation of the WHO analgesic ladder:

Figure 1.1 – The World Health Organization Analgesic Ladder



Treatment with acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen is widely accepted as first-line therapy in the management of pain. Milder opioid analgesic agents such as codeine are recommended in Step 2, while the more potent narcotic analgesics (morphine, oxycodone) are reserved for step 3.[31] Adjuvant therapy with antidepressants, anticonvulsants and muscle relaxants is also commonly observed in practice.

[31] Vielvoye-KerkmeerAPE, Mattern C, Uitendaal MP. Transdermal fentanyl in opioid-naive cancer pain patients: an open trial using transdermal fentanyl for the treatment of chronic cancer pain in opioid-naïve patients and a group using codeine. *Journal of Pain and Symptom Management*. 2000;19:185-192.

The National Guideline Clearinghouse ™ (NGC™), an initiative of the Agency for Healthcare Research and Quality (AHRQ) is a widely accepted source of clinical practice guidelines. AHRQ lists numerous guidelines that recommend opioids as an effective tool for the management of pain arising out of various mechanisms:[32,33 ,34]

1. Nociceptive pain - Nociceptive pain occurs subsequent to tissue damage caused by injury, and has a more defined pathology.[35] Painful stimuli are transmitted via nerve fibers to the central nervous system (CNS). Pharmacologic interventions such as nerve blocks and various analgesic agents are most commonly used to treat nociceptive pain.[36]

2. Neuropathic pain – Usually the pathological processes surrounding neuropathic pain may not be evident; however, the peripheral or central nervous systems play a role in the condition. Pain occurs in the absence of any obvious tissue damage. Neuropathic pain may also occur secondary to previous tissue damage, and is difficult to treat.[37] This form of pain is also associated with allodynia and hyperalgesia, which refer to pain in response to stimuli that do not normally elicit a painful response and a lowered tolerance for pain, respectively.[38] In addition to opioids, patients find adjuvant therapy with antidepressants and anticonvulsants to be beneficial.[39]

Neuropathic pain has also been classified further as being nociceptive or non-nociceptive. Nociceptive nerve pain occurs in response to damage to the nerve axon

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[32] Washington State Department of Labor and Industries. Guidelines for outpatient prescription of oral opioids for injured workers with chronic, noncancer pain. Olympia (WA): Washington State Department of Labor and Industries; 2002 Aug. 21 p.

[33] Dworkin RH, Backonja M, Rowbotham MC, et al. Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Archives of Neurolology.* 2003;60:1524-1534

[34] Registered Nurses Association of Ontario (RNAO). Assessment and management of pain. Toronto (ON): Registered Nurses Association of Ontario (RNAO); 2002 Nov. 142 p

[35] Cimino C. Painful Neurological Syndromes. In: Aronoff GM. Evaluation and Treatment of Chronic Pain. Baltimore, MD. Williams and Wilkins. 1992. MD.

[36] Burke SM, Weitz MA. Persistent pain in long term care: pathophysiologic mechanisms and treatment strategies. *The Consultant Pharmacist*. 2002;17SupplB:10-17.

[37] Cimino C. Painful Neurological Syndromes. In: Aronoff GM. Evaluation and Treatment of Chronic Pain. Baltimore, MD. Williams and Wilkins. 1992.

[38] Burke SM, Weitz MA. Persistent pain in long term care: pathophysiologic mechanisms and treatment strategies. *The Consultant Pharmacist*. 2002;17SupplB:10-17.

[39] American Geriatric Society Panel on Chronic Pain. The management of chronic pain in older persons. *Geriatrics*. 1998;53(suppl 3):S8-S24.

(inner information pathway of the nerve cell) or "depolarization of unmyelinated C-fibers" which is secondary to tissue damage. Non-nociceptive nerve pain occurs in response to lesions in the CNS, pain is usually associated with superficial tissues, and is not accompanied by inflammation. The variable response associated with opioid therapy in neuropathic pain may be indicative of the differences in underlying mechanisms. Consequently, debate about the clinical utility of opioids in neuropathic pain has been inconclusive. However, it is believed that opioid analgesics may be more effective in neuropathic pain syndromes that are nociceptive in nature.[40]

3. Mixed Nociceptive and Neuropathic pain – Examples of mixed pain syndromes include chronic recurrent headaches and vasculopathic pain syndromes. The underlying pathophysiology of these conditions is often unknown and treatment approaches are highly variable.[41] Consequently, treatment outcomes are highly unpredictable.

4. Psychogenic pain – Affective dimensions such as anxiety, fear, depression (i.e., emotions) and cognitive factors contribute to the occurrence of psychogenic pain. Psychiatric interventions may be useful in such situations.[42] Opioids are not recommended for use in these patients.

Failure of other therapeutic alternatives (NSAIDs, etc.) in opioid-naïve patients is also an indication for the use of narcotic analgesics in patients with chronic pain. Typically for opioid-naïve patients with unbearable pain, short-acting opioid medications such as hydrocodone or oxycodone (10 to 15mg), hydromorphone (2 to 4mg), codeine (30 to 60mg) and morphine (15 to 30mg) may be initiated. In addition to opioids, the use of antidepressants among pain patients has resulted in improved outcomes. Research has consistently shown that multidisciplinary approaches to the management of chronic pain are not only suitable but also preferred. However, there is little consensus regarding "patient selection and exclusion criteria," utilization of

[40] Dellemijn PL, Vanneste JAL. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. *The Lancet*. 1997;349:753-758.
[41] Ibid.
[42] Burke SM, Weitz MA. Persistent pain in long term care: pathophysiologic mechanisms and treatment strategies. *The Consultant Pharmacist*. 2002; 17(suppl B):10-18.

narcotic analgesics and sedative-hypnotics, and use of invasive techniques or implantation of devices across guidelines.[43]

1.3.4.1 Guidelines for Opioid Therapy in Chronic Non-malignant Pain Patients

The American Academy of Pain Management (AAPM) and the American Pain Society (APS) advocate the use of a comprehensive plan for practitioners treating pain with opioids.[44] The New Hampshire Board of Medicine G recommends a similar strategy.[45]

The plan involves conducting extensive patient-history evaluations, setting goals with periodic reviews, obtaining informed consent, keeping detailed records, and complying with state and board licensure requirements.

Other guidelines state that long-acting narcotic medications are effective pharmacological treatments for chronic persistent pain.[46,47] Management of episodic pain with short-acting narcotic medications contribute to improving outcomes. Adverse-events such as constipation and nausea that may arise from treatment with opioids must be treated and carefully monitored.

1.3.5 Treatment Options for Chronic Pain Syndrome Patients

Sanders and colleagues utilized an evidence-based approach to document the usefulness of various treatment modalities in the treatment of chronic pain

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[43] Sanders SH, Rucker KS and Anderson KO et al., Clinical practice guidelines for chronic non-malignant pain syndrome patients. *Journal of Back and Musculoskeletal Rehabilitation.* 1995;5:115–120.

[44] American Pain Society. The Use of opioids for the treatment of chronic pain. A consensus statement from American Academy of Pain Medicine and American Pain Society. Available at: http://www.ampainsoc.org/advocacy/opioids.htm. Accessed on Feb 22, 2003.

[45] New Hampshire Medical Society. Guidelines for the use of controlled substances in the treatment of pain. Available at: http://www.nhms.org/advocacy/pain.html. Accessed on November 11, 2002

[46] Washington State Department of Labor and Industries. Guidelines for outpatient prescription of oral opioids for injured workers with chronic, noncancer pain. Olympia (WA): Washington State Department of Labor and Industries; 2002 Aug. 21 p.

[47] Burke SM, Weitz MA. Persistent pain in long term care:pathophysiologic mechanisms and treatment strategies. *The Consultant Pharmacist*. 2002;17(SupplB):10-18.

syndrome.[48] In order for a particular recommendation or therapy to be included as part of the guideline, the therapy must have been evaluated in at least two well-designed, prospective research studies with large samples ($n \geq 200$). Similarly, a meta-analysis demonstrating effectiveness of a treatment modality was considered to meet evidence criteria.

NSAIDs, antidepressants, and anticonvulsants are believed to be useful in the management of chronic painful conditions. The literature review elicited promising yet inconclusive evidence about the usefulness of opioids and sedative-hypnotics among CPS patients. According to Sanders et al., there is a need for studies evaluating the long-term efficacy and safety of opioids and sedative-hypnotics among patients with chronic pain syndromes. There is a need for well-controlled, randomized trials evaluating various outcomes including cognitive function among various groups of CPS patients. "If long-term opioid or sedative-hypnotic medications are considered with chronic non-malignant pain syndrome patients, they should be applied only when there is clear evidence that they do not impair the patient but produce significant and sustained improvement in function."[49]

Physical and occupational therapy play an important role in restoring function, however, evidence indicates that the effects of these interventions are not sustained. These interventions are very important in helping patients improve posture, strength, and flexibility. Various behavioral and psychological interventions have consistently proven to be effective in certain groups of CPS patients and are of extreme importance. Programs that provide vocational guidance and techniques to cope with disability can enable functional restoration, but these services are often separate than those provided by a physician.[50]

The literature indicates that trigger point injections, botulinum toxin injections, and nerve block injections are of limited utility and should not be used routinely in CPS patients. Systematic, well-controlled studies evaluating long-term outcomes of

[48] Sanders SH, Rucker KS and Anderson KO et al., Clinical practice guidelines for chronic non-malignant pain syndrome patients. *Journal of Back and Musculoskeletal Rehabilitation.* 1995;5:115–120.
[49] Ibid.
[50] Ibid.

nerve blocks in this population are needed. Surgery is not recommended in the absence of "progressive neurological deficits, such as loss of bladder/bowel function or paralysis," or spine instability that must be corrected, or other findings such as "new lesions" in the patient.[51]

Physicians must educate patients with various aspects of their condition. In order to achieve optimal outcomes, patients must independently chart their progress, while discussing any barriers that might limit treatment success with the physician. The primary goals of treatment include improvement in patient's functional status and better ability to manage their pain. Even though patients on medications may exhibit a lack of subjective pain relief, the aforementioned goals of functional restoration should be stressed upon. Some other treatment objectives include minimizing abuse/overuse and dependence on pain medications (particularly opioids and sedative hypnotics), increasing rate at which patients return to work and other social activities, reducing pain intensity, and reducing utilization costs associated with the pain condition.

1.3.6 Opioids in Chronic Non-Malignant Pain

1.3.6.1 Narcotic Analgesic Classification

The narcotic analgesics are classified as agonists (oxycodone, morphine, fentanyl), and mixed agonist-antagonists, which are antagonists with analgesic action at the opiate receptors (buprenorphine, butorphanol, nalbuphine). This classification is based on the site of action of opioid analgesics: μ, δ, and κ receptors. Activation of μ receptors produces analgesia, respiratory depression, reduced GI motility, and euphoria, while activation of κ receptors produces analgesia, dysphoria, and psychotomimetic effects. Effect of δ receptor activation in humans is not clear.[52]

According to a clinical update published by the International Association for the Study of Pain in 1995, there was very little scientific evidence about the relative

[51] Ibid.
[52] Drug Facts and Comparisons. 57th Edition. 2003. Facts and Comparisons. St. Louis, MO. 2003.

risks and benefits of opioid therapy in chronic non-malignant pain.[53] In reference to opioid therapy, the organization continues to maintain that "we are still looking for a balanced approach, and outcomes-based guidelines remain only a hope for the future."[54]

Use of opioids among cancer patients has produced successful outcomes with limited adverse effects. The limited negative health outcomes such as analgesic tolerance, physical dependence, and addiction among cancer patients spurred speculation about the usefulness of opioid analgesics in other patient groups.[55] Despite the positive evidence regarding opioids in cancer pain, there is considerable controversy surrounding the use of narcotic analgesics in chronic pain conditions of non-malignant origin. Proponents of opioid use in these patients believe that political pressure, strict regulatory oversight, and an exaggerated fear of addiction and other side-effects have limited the use of these drugs, contributing to the under treatment of pain.[56] Despite the controversy, 90 percent of all opioid prescriptions in the United States are intended for pain relief in non-malignant chronic pain.[57]

1.3.6.2 Disadvantages of Narcotic Analgesics

Several adverse effects such as cognitive impairment, sedation, respiratory depression, nausea, constipation, edema, and hypogonadism have been associated with the use of opioids.[58] Cognitive impairment, respiratory depression, tolerance, abuse, and dependence associated with narcotic analgesics are the main factors implicated in the controversy surrounding opioid-therapy prescribed in the treatment of chronic non-cancer pain.

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[53] International Association for the Study of Pain. Opioids for chronic noncancer pain. 1995;3. Available at:: http://www.iasp-pain.org/PCU95c.html. Accessed on February 22.2003.
[54] International Association for the Study of Pain.The future: will pain be abolished or just pain specialists. 2000;8. Available at:: http://www.iasp-pain.org/PCU00-6.html. Accessed on October 11, 2002.
[55] Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *Journal of Pain and Symptom Management.* 1996;11:203-217.
[56] American Geriatric Society Panel on Chronic Pain. The management of chronic pain in older persons. *Geriatrics*. 1998;53(suppl 3):S8-S24.
[57] Brookoff D. Chronic pain:. The case for opiods. *Hospital Practice*. 2000;35;69-72,75-76,81-84.
[58] Bartleson JD..Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review. *Pain Medicine*. 2002;3:260-271.

Respiratory depression secondary to opioid use is not generally observed in clinical settings. Studies have shown that opioids produce different effects in the laboratory setting (pain free subjects) as compared to clinical settings.[59] It is believed that among patients, pain impulses are transmitted to respiratory centers, thereby inhibiting the depressive effect of opioids. In the case of healthy subjects (no pain) or situations wherein pain relief is brought about, for example, by a nerve block, impulse transmission is prevented, which could then result in respiratory depression with an equianalgesic opioid dose. Thus, pain serves as a physiological antagonist to opioid depressant effects. The upward titration of an opioid dose is safe provided the patient is experiencing pain.[60]

"Tolerance is a state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug's effects over time."[61] Tolerance may develop to both the analgesic and respiratory depressive effects of opioids; however, tolerance usually develops quicker in the latter case. There are no maximum opioid analgesic dose limits that have been established.

"Addiction is a primary, chronic, neurobiologic disease, with genetic, psychosocial, and environmental factors influencing its development and manifestations."[62] Addiction is characterized by impaired control, compulsive behavior, craving, and persistence with behaviors that are harmful.[63] In addition to brain chemistry, genetics and social/environmental cues play a role in the development of addictive behaviors. "Family history of addiction," "temperament," "poor support," and "drug availability," contribute to the development of addiction.[64] The literature lacks well-controlled studies that examine the potential for addiction with the long-term use of opioid analgesics. In the few studies that examine addiction

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[59] McQuay H. Opioids in pain management. *Lancet*. 1999;253:2229-2232
[60] Hanks GW. Pain, the physiological antagonist of opioid analgesics. *Lancet*. 1984;323:1477-1478.
[61] Liaison Committee on Pain and Addiction. Definitions related to the use of opioids for the treatment of pain. American Pain Society. Available at: http://www.ampainsoc.org/advocacy/opioids2.htm, Accessed, January 21, 2003.
[62] Ibid.
[63] Nedeljkovic SS, Wasan A, Jamison RN. Assessment of efficacy of long-term opioid therapy in pain patients with substance abuse potential. *The Clinical Journal of Pain*. 2002;18:S39-S51.
[64] Ibid

rates, the proportion of chronic non-cancer pain patients who develop addiction is very small. Most patients who develop addiction also have a history of substance abuse.

"Substance abuse is the use of any substance(s) for non-therapeutic purposes; or use of medication for purposes other than those for which it is prescribed."[65] Abuse associated with opioid use is of concern. Important issues to consider are the misuse of prescription opioids and the diversion of these drugs. An evaluation of overall prescribing patterns can serve as a guide to the existence and extent of the diversion problem. Patient histories with regard to pain history, drug abuse, and other pertinent information must be recorded. It is critical that all opioid prescribing be maintained by a single physician. Routine follow-ups to assess patient progress and medication use may also serve to identify problems with medication abuse.[66]

Data from the Drug Abuse Warning Network between 1990 and 1996 showed that use of opioids (fentanyl, morphine, meperidine, hydromorphone, and oxycodone) increased dramatically, except for meperidine. The number of drug abuse mentions as a proportion of use declined from 5.1 percent in 1990 to 3.8 percent in 1996.[67]

Pain patients often present with several psychiatric comorbidities. Retrospective data obtained through the Veteran's Administration (VA, n = 50) and a primary care clinic (PCC, n = 48) showed that the lifetime prevalence rates for depression (44% and 54%), anxiety (20% and 21%), alcohol abuse and/or dependence (46% and 31%), and narcotic abuse/dependence (18% and 38%) respectively, were substantial.[68] The highest rates of abuse were associated with oxycodone. A history of lifetime substance use disorder was strongly associated with abuse of narcotic analgesics.

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[65] The Federation of State Medical Boards of the Unites States, Inc. Model guidelines for the use of controlled substances for the treatment of pain. Available at: http://www.csam-asam.org/pain_treatment_guidelines.htm. Accessed, January 31, 2003.

[66] International Association for the Study of Pain. Opioids for chronic noncancer pain. 1995;3. Available at: http://www.iasp-pain.org/PCU95c.html. Accessed, October 11,2002.

[67] Joransons DE, Ryan KM, Gilson AM, Dahl JL. Trends in medical use and abuse of opioid analgesics. *JAMA*. 2000;283:1710-1719.

[68] Carrington M, Engles-Horton LL, Weber MB, et al. Use of opioid medications for chronic noncancer pain syndromes in primary care. *Journal of General Internal Medicine*. 2002;17:173-179.

Prolonged opioid therapy or large doses may cause neurotoxicity, which is characterized by cognitive impairment, cognitive failure, severe sedation, hallucinosis, myoclonus, seizures and hyperalgesia.[69] However, these symptoms are typically observed in extremely sick, dehydrated patients and in patients with renal impairment.

1.3.6.3 Long-Acting Narcotic Analgesic Therapy

Opioids that are available as prolonged delivery dosage forms (e.g., Oxycontin®, Avinza®, Duragesic®) have an improved safety profile compared to the short-acting opioid agents. Sustained release therapy is indicated for those patients with a successful trial on short-acting opioid agents.[70] Dosage should be adjusted to be similar to the average daily dose of the short-acting agent that provided adequate pain relief. There are numerous advantages associated with long-acting opioid dosage formulations: withdrawal and rebound symptoms are avoided; sedative effects that might occur after administration of short-acting agents are avoided due to optimal titration; normal sleeping patterns can be restored; optimal serum levels of drug are achieved thereby avoiding sub/supra analgesic doses; adherence to regimen is easier; abuse potential is minimized; patients can achieve greater control thereby allowing them to focus attention away from pain. Empiric evidence suggests that abuse associated with opioid analgesics has increased from 1997 to 2002.[71] However, the proportion of drug abuse mentions for hydrocodone (a short-acting narcotic) were higher when compared with either fentanyl, oxycodone, or morphine. This study did not distinguish between long-acting and immediate release forms of morphine and fentanyl. Sustained release dosage forms may be more useful and preferred as

[69] Brevik H. Opioids in cancer and chronic non-cancer pain therapy – indications and controversies. *Acta Anaesthesiologica Scandinavica*. 2001;45:1059-1066.
[70] Ibid.
[71] Gilson AM, Ryan KM, Joranson DE, Dahl JL. A reassessment of trends in the medical use and abuse of opioid analgesics and implications for diversion control:1997-2002. *Journal of Pain and Symptom Management*. 2004;28:176-188.

compared to short-acting opioid agents.[72] In this study, the effect, the effect long-acting morphine, namely, Avinza® on various measures of pain and cognitive status will be examined.

The following steps are recommended when patients currently on opioids are being converted to the controlled release formulation:

1. Using standard conversion ratio estimates (see table below), multiply the mg/day of the previous opioids by the appropriate multiplication factors to obtain the equivalent total daily dose of oral morphine.
2. Round down to a dose that is appropriate for the capsule strengths available (30, 60, 90, 120 mg Avinza capsules)
3. Discontinue all other around-the-clock opioid drugs when controlled-release Avinza therapy is initiated.[73]

1.3.6.4 Morphine Sulfate Extended Release (Avinza):

Morphine-3-glucoronide and morphine-6-glucoronide are the active metabolites of morphine sulfate. MS Contin is the most widely used formulation of controlled release morphine. Avinza (morphine sulfate extended-release) capsules received marketing approval from the FDA March 2002 for "the once-daily treatment of chronic, moderate-to-severe pain in patients who require continuous, around-the-clock therapy for an extended period of time."[74] The drug delivery system is a technological advance as the capsule contains morphine in an immediate release form and a sustained release form. Once a stable plasma level of morphine is attained, the sustained release beads deliver the drug over a 24-hour period. Avinza is available in 30, 60, 90, and 100 mg capsules. A pharmacokinetic comparison between Avinza and MS Contin showed that Avinza provides maximum concentrations over a longer

[72] Bartleson JD..Evidence for and against the use of opioid analgesics for chronic nonmalignant low back pain: a review. *Pain Medicine*. 2002;3:260-271.
[73] Ibid
[74] Elan Corporation. FDA Approves Once-Daily Avinza (Extended Release Morphine) For Chronic Moderate-to-Severe Pain. http://www.docguide.com/news/content.nsf/news/8525697700573E1885256B830048A246. Accessed: Jun 8, 2003.

period of time with minimal fluctuations in concentration levels.[75] From a clinical perspective, a stable concentration of morphine has been associated with lower levels of pain intensity in chronic pain patients. The following directions must be followed when converting from conventional immediate-release oral morphine to controlled/extended/sustained release oral morphine: Administer 50 percent of the total daily morphine dose every 12 hours; one third of total daily dose administered every eight hours (MS Contin and extended release tablets only); or the full daily morphine dose every 24 hours (Kadian only).[76] The last conversion criteria can also be extended to Avinza.

Table 1.1 Equianalgesic Doses of Centrally Acting Opioid Doses Compared to Morphine

Drug	Dose (mg) oral[77,78,79]	Conversion Factor
Morphine	30	1
Codeine	200	0.15
Hydrocodone	30	1
Hydromorphone (Dilaudid)	7.5	4
Levorphanol	1	30
Methadone	4	7.5
Oxycodone	20	1.5
Oral transmucosal fentanyl citrate (Actiq)	1	30
Propoxyphene	130	0.23
Tramadol (Ultram)	150	0.2

[75] Portenoy RK, Sciberras A, Eliot L, Loewen G, Butler J, Devane J. Steady-state pharmacokinetic comparison of a new, extended-release, once-daily morphine formulation, Avinza™ and a twice-daily controlled-release morphine formulation in patients with chronic moderate to severe pain. *Journal of Pain and Symptom Management*. 2002;23:292-300.
[76] Drug Facts and Comparisons. 57th Edition. *Facts and Comparisons*. St. Louis, MO. 2003.
[77] Ibid
[78] CPSO Task Force on CNMP. Evidence-based recommendations for medical management of chronic non-malignant pain: reference guide for clinicians. College of Physicians and Surgeons of Ontario (CPSO). Ontario, Canada;2000.
[79] American Pain Society. Principles of analgesic use in the treatment of acute pain and cancer pain. 4th ed. Glenview, IL: American Pain Society; 1999.

1.3.7 Studies Assessing Safety and Efficacy of Opioid Therapy in Chronic Non-Malignant Pain

Evidence from a few studies indicate that non-malignant pain patients presenting at multidisciplinary clinics may find limited improvement with narcotic use and some may even benefit with elimination of narcotic therapy. McNairy and colleagues classified a sample of 50 chronic pain patients based on medication use as non-abusers (n = 14), abusers (n = 15), and dependent users (n=21).[80] The authors concluded that the two latter groups demonstrated impaired cognitive function. Finlayson et al. examined long-term outcomes in chronic pain patients that were treated for substance dependency.[81] Follow-up survey results showed that more patients who persisted with treatment for dependency (n = 34) reported improved work and social relationships as compared to those that discontinued treatment (n = 16). Reports of pain in the two groups showed no differences. At two-years, two patients who discontinued treatment reported being pain-free. However, there are numerous limitations associated with these studies. Patients in these studies were abusers or dependent users of prescription narcotics. The results are not generalizable to the entire population of pain patients. While one study reported pain levels at follow-up, McNairy and colleagues did not address pain as an outcome measure. Finally, the use of other drugs (e.g., benzodiazepines) that produce significant cognitive impairment was not reported. The conclusion that chronic pain patients may benefit from the discontinuation of opioid therapy seems erroneous in light of these limitations.

Results of studies documenting the efficacy of opioid therapy in neuropathic pain have shown a variable response. Portenoy concludes that opioid therapy may not be generally indicated; however, individual differences, and the possibility of a

[80] McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. *Pain*. 1984;18:169-177.
[81] Finlayson RE, Maruta T, Morse RM, Martin MA. Substance dependence and chronic pain: experience with treatment and follow-up results. *Pain*. 1986;26:175-180.

favorable outcome substantiate the use of narcotic analgesics.[82] More recent evidence indicates that neuropathic pain is responsive to opioid therapy.

A review of studies examining the efficacy of narcotic analgesics in chronic pain indicates that these drugs have an important role in the management of chronic non-malignant pain, particularly after other therapeutic options have been exhausted. These studies are presented in a reverse chronological order below:

The morphine responsiveness, efficacy, and tolerability in patients with non-tumor associated pain (MONTAS) trial was a prospective, double-blind, placebo controlled, crossover trial in which non-tumor associated (NTAS) pain patients (n = 49) were assigned to group I (10 and 30 mg doses of SR-morphine for one week followed by placebo in the second week) or group II (placebo was followed by SR-morphine).[83] Patients with neuropathic (n = 33) and nociceptive pain (n = 15) who had been exposed to a variety of treatment options without adequate relief participated in the trial, while one patient was not included due to a stroke prior to administration of study medication. All of the patients had a "long history of severe pain," "polymedication, many with step II opioids," "a high incidence of increased disability and psychological disturbances, resulting in social and even financial problems." At the end of the trial, patients were categorized as responders if they reported a 50 percent improvement in pain or pain intensity was less than 5 on a numerical rating scale, pain was tolerable or minimal (visual rating scale < 3), and side effects were manageable while on morphine. In order to be classified as a partial responder, side effects should have been manageable, while some pain relief was obtained due to placebo and inadequate pain relief was obtained due to study drug.

Among patients that reported no pain/good analgesic response, 19 were on morphine while three were on placebo. Mean improvement in pain intensity was 33 percent for morphine compared to seven percent for placebo. An approximately

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[82] Portenoy RK. Opioid therapy for chronic nonmalignant pain: a review of the critical issues. *Journal of Pain and Symptom Management*. 1996;11:203-217.

[83] Maier C, Hildebrandt J, Klinger R, Henrich-Eberl C, Lindena G. Morpine responsiveness, efficacy, and tolerability in patients with chronic non-tumor associated pain – results of a double-blind placebo-controlled trial (MONTAS). *Pain.* 2002;97:223-233.

equal number of patients on morphine (n = 17) and placebo (n =16) reported that pain was just tolerable. Significantly more patients treated with morphine (n = 19, 40%) than with placebo (n = 1, 2%) were classified as responders. In addition to pain intensity, improvements in affect, mood, and sleep quality were also observed. A greater proportion of patients on morphine (58.0%) experienced side-effects as compared to those on placebo (22.0%), however, some of these side effects were also associated with opioid withdrawal and a greater reliance on rescue medication during the placebo phase. Most patients (58.3%) relied on the maximum daily dose (180mg) of morphine allowed in the trial. More patients with neuropathic pain (14 of 33, 42%) were categorized as responders than patients with nociceptive pain (3 of 15, 20%). The proportion of partial responders was greater in the nociceptive pain group (40%) than in neuropathic pain group (33.33%). In addition to analgesia, responders to morphine reported improvements in mood, sleep quality, pain disability, and scores on depression and exercise endurance improved as well. "The sum score of central nervous system (CNS) complaints were increased only in the non-responders, but lowered in the response group and during morphine therapy."[84]

Attal and colleagues examined the efficacy of IV morphine in a sample of patients (n = 15) with central pain (neuropathic pain subsequent to stroke or spinal cord injury).[85] Eligibility criteria included opioid-naive patients with moderate pain (>30/100 at baseline) that had persisted for six or more months. The study utilized a double-blind placebo-controlled trial in which patients were either randomized to receive morphine (tolerability to the drug was assessed in a previous titration phase) or 0.9 percent saline. Responders and partial responders to treatment were defined as those patients who reported 100 percent and 50 percent relief from pain, respectively. Patients treated with morphine reported on average that spontaneous pain reduced by 46.42 percent 30 minutes after injection (mean = 61.6 mm, s.d. = 17 to mean = 33mm, s.d. = 23), while patients receiving placebo reported a 24 percent reduction on

[84] Ibid.
[85] Attal N, Guirimand F, Brasseur L, Gaude V, Chauvin M, Bouhassira D. Effects of IV morphine in central pain. *Neurology*. 2002;58:554-563.

average (mean = 69 mm, s.d. = 16.9 to mean = 52mm, s.d. = 19). A greater proportion of patients treated with morphine (46%) achieved a 50 percent or greater reduction in pain as compared with placebo (13%). Among patients experiencing allodynia (n =10) at baseline, nine patients achieved a 50 percent or better reduction in pain intensity with morphine and three patients achieved this outcome with placebo. Morphine did not improve tolerability to mechanically induced thermal or electric stimuli. A total of 14 patients were successfully switched to sustained-release oral therapy with morphine, and six discontinued the treatment due to adverse effects. A significant reduction (mean difference = 20 mm, p = 0.03, n = 8) in pain intensity was reported on average at the end of four weeks of oral therapy. Long-term followup (≥ one year) showed that only three patients continued to find relief with morphine while three discontinued due to side effects. More patients discontinued treatment due to the concern about side-effects than lack of pain relief. The results suggest that morphine is effective in some neuropathic pain syndrome patients, but long-term side effects may pose a problem for many patients.

A randomized cross-over trial was utilized to assess patient preference for either sustained release morphine (MS Contin) or transdermal fentanyl (Duragesic®).[86] In order to be included in the trial, patients should have received opioids for six weeks and achieved moderate relief with a stable opioid dose for one week prior to the study. Overall, a significantly greater number of patients either strongly preferred or preferred fentanyl patches (n = 138, 65%) over SR morphine (n = 58, 28%). Better pain relief and ease of dosing were cited most commonly as advantages of fentanyl over morphine. More patients on fentanyl rated pain relief as good or very good, regardless of whether patients experienced nociceptive pain (43/123, 35%), neuropathic pain (21/62, 34%), or mixed nociceptive and neuropathic pain (23/63, 37%). As per the corresponding classification, the proportion of patients that provided similar ratings with the use of SR morphine were 25 percent (15/59), 23 percent (27/116), and 20 percent (12/59), respectively. Average pain intensity ratings

[86] Allan L, Hays H, Jensen NH, et al. Randomised crossover trial of transdermal fentanyl and sustained release oral morphine for treating chronic non-cancer pain. *British Medical Journal.* 2001;322:1-7.

were significantly lower ($p < 0.001$) with fentanyl (57.8 cm, range – 33.1 to 82.5) than with SR morphine (62.9, range – 41.2 to 84.6). On average, patients receiving fentanyl provided significantly higher ratings on most SF-36 subscales, no significant differences in scores on the emotional subscales were observed. Among patients who had no prior exposure to opioids, withdrawals and reports of adverse events for both drugs were similar. Among patients who had prior exposure to morphine, a greater number of withdrawals occurred when patients were treated with fentanyl first. It was concluded that the higher proportion of withdrawals occurred due to larger doses resulting in more unanticipated side-effects.

Wilder-Smith et al. compared the effects of controlled release (CR) tramadol (n = 28), (CR) dihydrocodeine (n = 29), and NSAIDs (n = 30) in patients with pain due to osteoarthritis.[87] Opioid treatment groups were permitted to continue using corresponding immediate release formulations for breakthrough pain. Patients in the opioid treatment arms provided higher pain intensity ratings than the control group at baseline. Pain intensity at rest was significantly lower in the tramadol group ($p = 0.04$). Pain intensity ratings at baseline were significantly higher than those obtained during treatment. Quality of sleep ratings improved from poor at baseline to "good" and "very good" for the dihydrocodeine and tramadol groups respectively on day 28. However, no significant group differences emerged on this outcome measure. Pain due to osteoarthritis was adequately controlled with tramadol and dihydrocodeine. Use of breakthrough pain medication was limited.

Milligan and colleagues enrolled chronic non-malignant pain patients (n = 532) (persistent pain ≥ 6 weeks) who had a moderate response with opioids into an open-label trial to assess the safety, efficacy, and preference of fentanyl transdermal patch over other opioids.[88] A total of 301 patients (43%) completed the trial, which lasted

[87] Wilder-Smith CH, Hill L, Spargo K, Kalla A.. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAIDs: a randomized study comparing analgesia, antinociception and gastrointestinal effects. *Pain*. 2001;91:23-31.

[88] Milligan K, Lanteri-Minet M, Borchert K, et al. Evaluation of long-term efficacy and safety of transdermal fentanyl in the treatment of chronic noncancer pain. *The Journal of Pain*. 2001;2:197-204.

for 12 months. Average dose of fentanyl used increased from 48 μg/hour to 90 μg/hour in the last month of the trial. The proportion (71%) of responders to opioids at the start of the study did not vary significantly from the proportion (67%) at the end of the study. In response to items on the SF-36, more patients reported pain to have improved from very severe/severe to moderate at the end of the study. Overall improvements in QOL (physical, social, and mental) were minor, yet fentanyl proved tolerable and produced analgesia among patients with nociceptive and neuropathic pain.

A medical record examination of primary care clinics in the Wisconsin area showed that a broad range of conditions such as low back/lumbar pain, arthritis, headache/migraine, neck/upper back, fibromyalgia, etc. are treated with narcotic analgesics.[89] A total of 209 chronic pain patients were identified from a population of 83,000 patients that received care at five centers. The chronic pain patients received the following narcotic analgesics for at least three months: Percocet (30%), Extended release morphine tablets (20%), Vicodin (14%), Tylenol #3 (14%), Oxycontin (11%), Oxycodone (10%), Methadone (8%), Darvon (9%). (Proportion of narcotics used by these patients exceeds 100 since some patients used more than one narcotic medication). A diagnosis of depression was confirmed in 37.8 percent of the sample (n = 79). A significantly greater number of positive diagnoses for depression were made in individuals under age 60 and women. Depression, in addition to panic and anxiety disorders was most commonly associated with headaches/migraines. Patients were most commonly treated with opioids for chronic pain due to lumbar/low back pain (37%), fibromyalgia (26%), and headache/migraine (23%). The high prevalence of chronic pain in the US, relatively few patients (0.25%) with prescriptions for opioids in the population studies, and the increased acceptance of the use of opioids in chronic non-malignant pain patients led the authors to conclude that pain is under-treated in the primary care setting examined for this study. In addition to concerns

[89] Adams NJ, Plane MB, Fleming MF, Mundt MP, Saunders LA. Opioids and the treatment of chronic pain in the primary care setting. *Journal of Pain and Symptom Management.* 2001;22:791-796.

about side effects and addiction, "lack of knowledge regarding pain management," inability to assess pain, and concern about regulatory authorities were cited as barriers to physician acceptance of long-term opioid therapy as an acceptable option in the treatment of chronic pain.

Roth and colleagues conducted a double-blind placebo-controlled trial in which patients with moderate to severe pain due to osteoarthritis were assigned to receive controlled release (CR) oxycodone 20mg/day (n = 44), or 40 mg/day (n= 44), or placebo (n = 45).[90] The trial extended for a period of 14 days, subsequent to which patients were enrolled in an open-label drug study with follow-up measures reported at 6, 12, and 18 month intervals. A total of 39 patients discontinued therapy due to lack of pain relief; a significantly greater number of patients in the placebo group (n = 22) dropped out of the study than in the treatment groups (n = 17). A significantly higher proportion of patients discontinued treatment due to adverse effects from treatment (26/88) than from placebo (2/45). Patients receiving the largest dose of CR oxycodone reported significant improvements over baseline pain intensity ratings than the two other groups at the end of two weeks. Improvements in function (minimal functional impairment reported at baseline) were observed in the treatment groups, however, no statistical differences were detected in comparison with placebo. Among patients that continued the long-term trial, analgesic efficacy was observed for the length of the study (18 months) with a mean dose of 40mg/day of CR oxycodone. Withdrawal of drug resulted in return of pain to baseline levels, which further established the effectiveness of treatment. Improvements in sleep, sleep quality, and mood were also observed.

Taylor and colleagues conducted a retrospective review of 59 pain patients who were treated with methadone for an average duration of 18.4 months (s.d. = 28.5).[91] Of these patients, 14 remained on methadone (ON group), 19 were lost to follow-up, and 26 discontinued methadone treatment (OFF group). Among patients in the OFF

[90] Roth SH, Fleischmann RM, Burch FX, et al. Around-the-clock, controlled release oxycodone therapy for osteoarthritis-related pain. *Archives of Internal Medicine*. 2000;160:853-860.
[91] Taylor WF, Finkel AG, Robertson KR, et al. Methadone in the treatment of chronic nonmalignant pain: A 2 year follow-up. *Pain Medicine.* 2000;1:254-259.

group, the condition of three patients had resolved, six were non-compliant, eight did not achieve adequate pain relief, 12 experienced unmanageable side effects (peripheral edema and/or nausea), and four patients died. (Total exceeds 26 since more than one patient discontinued treatment for multiple reasons.). Only 50 percent (13/26) of patients that discontinued methadone sought and continued treatment with other opioids. Although significantly ($p < 0.05$) more patients ON methadone were employed (53%) than those OFF methadone (23%), this comparison does not reflect the proportion of patients on other opioids who returned to work. A general trend of dose increases were observed for all opioids indicating that long term opioid therapy would more often than not be accompanied by dose escalation. Patients that were switched from methadone to other opioids continued to derive significant benefit from narcotic analgesic therapy. The finding that more patients in the ON group were employed as compared to those in the OFF group prompted the authors to favor the use of long-acting opiod therapy in comparison with short-acting narcotic analgesic therapy from their practice experience:

1. The finding may be a manifestation of the negative impact on employment of the dysphoria associated with the use of short-acting opioids;
2. The relative disinterest of workers with dysphoria;
3. The increased absolute number of pills taken by less functional patients;
4. The utility of time-contingent dosing as opposed to symptom-based dosing.[92]

Caldwell et al. conducted a double-blind placebo-controlled trial to evaluate the effectiveness of CR oxycodone (Oxycontin® 10mg) and immediate release (IR) oxycodone-APAP (5/325mg) (Percocet®) in patients with moderate to severe pain due to osteoarthritis (OA) that were unresponsive to NSAID therapy.[93] All patients

[92] Ibid.
[93] Caldwell JR, Hale ME, Boyd RE et al. Treatment of osteoarthritis pain with controlled release oxycodone or fixed combination oxycodone plus acetaminphen added to nonsteroidal anti-inflammatory drugs: A double blind, randomized, multicenter, placebo controlled trial. *The Journal of Rheumatology.* 1999;26:862-869.

(n = 167) underwent a titration phase (30 days) prior to the randomization phase in which the dose of Percocet (maximum dose – 12 tablets/day) was adjusted to achieve pain relief without significant side effects. A total of 36 patients withdrew due to side effects and another 17 due to lack of analgesia. Among patients that continued the trial, mean dose of IR oxycodone was 40mg/day. Patients (n = 107) were randomized to one of three-treatment arms placebo (n = 36), Oxycontin (n = 34) (bid), and Percocet (n = 37) (qid). Global assessments for pain intensity (0 = none, 1 = slight, 2 = moderate, and 3 = severe) at joint determined to be most painful and quality of sleep (1 = very poor, 2 = poor, 3 = fair, 4 = good, 5 = excellent) were made. Patients on placebo experienced a significantly greater ($p < 0.0040$) increase in pain intensity (mean increase = 1.00, sd = 0.13) than either Oxycontin (mean increase = 0.44, sd = 0.13) or Percocet (mean increase = 0.49, sd = 0.11) than those reported at the end of titration phase. Global quality of sleep ratings declined dramatically ($p \leq 0.0001$) for the group receiving inactive treatment, while scores for groups receiving drug treatment showed no change. The two active treatments seemed to produce comparable results with respect to pain intensity, but patients reported better quality sleep with the CR dosage form.

Chronic low back patients (n=33) without structural pathology for their condition, history of substance abuse, or psychiatric disease who were refractory to other treatment options (physical therapy, psychotherapy, intraspinal injections, and adjunctive medications) were enrolled into an opioid trial.[94] Of these patients, five discontinued the trial due to side effects, seven did not respond to opioid therapy, and 21 showed significant improvement in pain and disability from baseline (numerical rating scale mean = 8.45, range 6 to 10; Oswestry disability scale score mean = 64, range – 42 to 88) to conclusion of trial (mean = 4.90, range – 0 to 8; mean = 50, range – 9 to 80). Patients that obtained benefit from the trial received long-term opioid therapy (mean duration – 32 months). A comparison between the responders (n = 21) and all the other patients (n =12) at the end of one-year showed that on average, pain

[94] Schofferman J. Long-term opioid analgesic therapy for severe refractory lumbar spine pain. *The Clinical Journal of Pain*. 1999;15:136-140.

scores and disability scores improved by 3.6 and 13.8 points, respectively in the former group and remained stable in the latter group. The author was unable to identify any specific variables that may have contributed to the analgesic efficacy of opioids in one group of patients (n = 21) and the lack of effect in a similar subgroup (n =7).

Jamison et al. conducted a randomized, open-label, long-term study to evaluate the effectiveness of opioids in chronic non-malignant pain patients with moderately severe back pain (pain intensity ≥ 40 on scale ranging from 1 to 100). In the first phase of the study, patients were randomized to one of three treatment regimens, i.e., naproxen (maximum daily dose – 1000mg), fixed dose oxycodone (Roxicodone® maximum daily dose – 20mg), and a titrated dose of oxycodone and SR morphine (Oramorph SR®).[95] Patients were followed for 16 weeks after which all patients were eligible to receive oxycodone and SR morphine (maximum daily dose – 200mg) for an additional 16 week period. In the final phase of the study, opioid dose was gradually tapered for 12 weeks, followed by a 4-week washout period, at the end of which final follow-up measures were obtained. Information on pain intensity, sleep and activity, participation in activities with family, socioeconomic factors, and previous medication history was collected by using the Comprehensive Pain Evaluation Questionnaire (CPEQ), which is an amalgam of several exhaustive instruments. Additionally, the SF-36 and the SCL90-R were administered at baseline and 1-year follow-up.

Of the 36 participants, 74.3 percent had undergone prior surgery to treat their low back pain.[96] At baseline, the group receiving titrated doses of opioids reported greater number of hours reclining ($df = 16$, $F = 4.65$, $P < 0.05$) than the other groups. Side effects were common in the opioid treatment groups ($p < 0.001$), and characteristics of participants reporting frequent adverse events included more severe pain ratings at baseline ($r = 0.44$, $p < 0.01$), higher likelihood of compensation ($r =$

[95] Jamison RN, Raymond SA, Slawsby EA, Nedelijkovic SS, Katz NP. Opioid therapy for chronic noncancer back pain. *Spine*. 1998;23:2591-2600.
[96] Ibid.

0.36, $p < 0.05$), frequent users of nicotine products ($r = 0.35$, $p < 0.05$), and a sedentary lifestyle. Although the NSAID group reported higher levels of anxiety, other emotional variables such as depression and irritability did not differ across groups. At the end of 16 weeks, average pain intensity rating increased from 64.3 (s.d. = 17.50) to 65.5 (s.d. = 19.5) in the naproxen group, and improved from 67.2 (s.d. = 15.12) to 59.8 (s.d. = 16.65) in the fixed dose group and from 70.8 (s.d. = 18.45) to 54.9 (s.d. = 15.87) in the SR morphine group. Current pain intensity ratings did not change for the naproxen group, but reduced from 62.3 (s.d. = 17.83) and 68.2 (s.d. = 23.25) to 55.3 (s.d. = 20.87) and 51.3 (s.d. = 18.98) in the oxycodone and SR morphine groups respectively. Highest and lowest pain intensity ratings, anxiety, depression, and irritability scores were significantly lower for the opioid groups compared to the naproxen group. There were no significant group differences in pain, mood, activity, and sleep at the end of the study period. A consistent feature was that patients reported moderate levels of pain intensity at the end of the trial. Although opioids improved patient mood and pain, no significant impact was observed on the extent to which participation in activities increased.

Watson and Babul conducted a randomized, double-blind, placebo controlled, crossover trial that examined the effectiveness of sustained release oxycodone (10mg) in patients with postherpetic neuralgia.[97] In addition to the study drug, patients were permitted to continue taking concurrent medications such as NSAIDs and antidepressants. " A previous study in postherpetic neuralgia suggested that standard deviations of 27mm (pain VAS) were reasonable to expect. With the patient serving as his or her own control, and assuming a minimal correlation between responses in a single subject in the two treatment periods, a total of 30 completed patients would provide 80% power ($\beta = 0.2$) to detect a difference of 20mm in pain intensity VAS at a statistical significance of 0.05."[98] A total of 50 patients were enrolled, and 38 completed the trial. Patients served as their own controls and measures on pain

[97] Watson CP, Babul N. Efficacy of oxycodone in neuropathic pain: a randomized trial in postherpetic neuralgia. *Neurology*. 1998;50:1837-1841.
[98] Ibid.

intensity (100mm VAS) and categorical pain intensity scale (0 - no pain, 1 – mild pain, 2 – moderate pain, 3-severe pain, 4 – unbearable pain) were obtained at the end of each four-week interval. Pain relief was measured on a six point scale (0 – pain worse, 1 – no relief, 2 – slight relief, 3 – moderate relief, 4 –a lot of relief, 5 – complete relief.). A total of eight participants withdrew due to side-effects, five while on oxycodone and three while on placebo. Reports of average pain intensity, both VAS (35mm +/- 25 vs 54mm +/-25mm) and categorical scale (1.7 +/- 0.7 vs 2.3 +/- 0.7) were significantly lower ($p < 0.001$) during the fourth week for patients being treated with oxycodone than with placebo. Oxycodone rather than placebo was associated with greater pain relief and lower disability scores ($p < 0.0001$). BDI scores remained unchanged throughout the trial. Results from this study show that opioid analgesics (oxycontin) are effective in the management of neuropathic pain, particularly postherpetic neuralgia.

Dellemijn and Vannaste conducted a double-blind crossover trial to assess the efficacy of intravenous fentanyl in chronic pain patients (nociceptive nerve pain, deaffrentation pain, and mixed neuropathic pain).[99] Patients experiencing pain due to trigeminal neuralgia or pain of ambiguous origin were not included in the study. All patients reported baseline pain intensity scores and were then infused with fentanyl and diazeapam (inert placebo). After one week (washout period), patients with moderate to severe pain (≥ 40 on NRS) were subsequently randomized to receive fentanyl (5μg/ml) and diazepam (0.2mg/ml). All patients in group-1 ($n = 26$) received either the drug first or active placebo first, while patients in group-2 ($n = 24$) received drug (fentanyl - 5/ml) first or inactive placebo (saline) first. Depression scores indicated that all patients were either severely ($n = 44$) or moderately ($n = 6$) depressed. Although patients reported greater pain relief with fentanyl, no significant differences were detected in percent pain intensity difference (PID) or percent pain unpleasantness difference (PUD) between fentanyl, diazepam, or saline. Average

[99] Dellemijn PL, Vanneste JAL. Randomised double-blind active-placebo-controlled crossover trial of intravenous fentanyl in neuropathic pain. *Lancet*. 1997;349:753-758.

dose of fentanyl and diazepam that was infused equaled 873µg (equivalent morphine dose – 70mg) and 52.1mg respectively, over five hours. The proportion of respondents (≥ 50% pain relief) to fentanyl (65.4% and 50.0%) was significantly greater in group 1 and 2 respectively, than with diazepam (15.4%) or placebo (8.3%). No differences were apparent between diazepam and saline with respect to pain intensity.

Dellemijn and colleagues extended the previous study to examine long-term use of transdermal fentanyl by soliciting volunteers who successfully completed the trial reported above. Only patients with chronic neuropathic pain were solicited for the trial.[100] Pain intensity and unpleasantness evaluations were made for each of the 12 weeks of the trial. In addition to pain intensity and unpleasantness, self reported measures were obtained on the Zung depression scale, and a validated quality of life index that incorporated three dimensions: "symptom control," "physical well-being," and "psychological well being." At the end of this period patients were gradually weaned off fentanyl by lowering the dose to 25 µg/hour and then switching patients to 60mg/day sustained release morphine, which was finally discontinued. A total of 48 patients participated in the study, and 30 completed the trial. Of these 30 patients, 13 (43.33%) experienced greater than 50 percent relief in pain intensity, while the rest experienced less than 50 percent relief. The greater relief in pain intensity was also associated with a reduction in psychological symptoms. Among the nine patients who continued transdermal fentanyl therapy at the end of 2 years, average pain intensity difference was 47 percent, with 3 patients obtaining negligible pain relief. Patients adapted to the drug treatment within a week, which was accompanied by a corresponding reduction in side-effect severity and sedation. Although many patients obtained substantial pain relief, a majority (82%) did not continue treatment with fentanyl. Pain relief was not associated with QOL scores or ratings obtained on the Zung depression scale. Side-effects of the treatment in many cases outweighed the

[100] Dellemijn PL, Duijn HV, Vanneste JAL. Prolonged treatment with transdermal fentanyl in neuropathic pain. *Journal of Pain and Symptom Management*. 1998;16:220-229.

benefits of pain relief. Successful treatment with intravenous fentanyl was a predictor of good outcome with transdermal therapy.

Moulin DE and colleagues conducted a randomized double-blind, placebo-controlled trial to assess the effectiveness of SR morphine in chronic pain patients (persistent pain ≥ 6 months).[101] Patients who were unresponsive to NSAIDs and tricyclic antidepressants (TCAs) with moderate pain ratings in the week prior to the trial (pain intensity ≥ 5 cm on a 10cm long VAS) were included in the trial. Almost all patients (60/61) had used codeine in the past (mean dose- 126.5mg, mean duration – 32.3 months). Patients were titrated upto a maximum dose of 60mg MS Contin bid for 3 weeks, followed by a maintenance dose in the evaluation phase, which lasted for 6 weeks. Benztropine was administered as placebo. Following a two-week washout period, patients were crossed over to corresponding treatment and placebo arms. The following subject-rated measures were obtained: SCL-90, Profile of Mood States (POMS), sickness impact profile (SIP), and the Pain Disability Index (PDI). Impact on cognitive ability was assessed with the High Sensitivity Cognitive Screen. Pain intensity, pain relief, and adverse effects, which were measured on a three-point scale that ranged from mild to severe, were obtained on a weekly basis. Psychological and functional status assessments were made at the end of titration, follow-up, and washout phases. "A sample size of 42 was determined to be sufficient to detect a difference of 1cm with a standard deviation of 2 cm to provide 90 percent power at the 0.05 significance level." Pain intensity ratings reduced significantly ($p = 0.02$) for the group treated with morphine first and the effects persisted with placebo. Patients who were assigned to receive placebo first failed to respond to both treatments. Psychological and functional status assessments did not improve in response to treatment with morphine. Prior exposure to codeine may have resulted in the limited usefulness of current therapy; however, the average morphine dose used in the study (83.5 mg) was equivalent to four times that of the average codeine dose (560 mg) that

[101] Moulin DE, Iezzi A, Amireh R, et al. Randomized trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147.

patients were using before the trial. Morphine dose of 120mg per day did not adversely affect cognitive abilities such as memory, attention, and concentration.

Arkinstall and colleagues utilized a randomized double-blind, placebo-controlled crossover study design, which showed that controlled release codeine (Codeine Contin®) on average was more effective than placebo in reducing pain intensity VAS scores (35 mm s.d. = 18 vs 49mm s.d. = 16mm) among a sample of chronic non-malignant pain patients.[102] The amount of rescue medications for breakthrough pain was significantly lower while patients were on CR codeine than on placebo.

A 24-hour patient-controlled analgesia technique was used to assess the efficacy of IV morphine in nociceptive, neuropathic, and mixed pain of chronic non-malignant and cancer origin.[103] Of the 22 patients included in the study, 12 achieved a good response (> 70mm pain relief on a 100mm VAS scale and few side effects), four patients achieved a moderate response (<70mm and >30mm pain relief at two or more assessment times), and the rest achieved a poor response (< 30mm pain relief and intolerable side effects). Response to opioids was variable regardless of type of pain and source of pain suggesting that management of certain pain syndromes (e.g., neuropathic pain syndromes) with opioids should not be excluded as a possibility.

Bouckoms et al. conducted a retrospective review of 59 patients that had been prescribed narcotic analgesics for chronic nonmalignant pain a period of 36 months.[104] A total of 20 patients (34%) obtained complete relief and another 27 patients (46%) obtained partial relief with narcotic analgesic use. Nociceptive pain was responsive to opioids, while neuropathic pain, drug abuse, and comorbid depression were not associated with improvement in pain. Comorbidities such as

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[102] Arkinstall W, Sandler A, goughnour B, Babul N, Harsanyi Z, Darke AC. Efficacy of controlled –release codeine in chronic non-malignant pain: a randomized, placebo-controlled clinical trial. *Pain.* 1995;62:169-178.

[103] McQuay HJ, Jadad AR, Carroll D, Faura C, Glynn CJ, Moore RA, Liu Y. Opioid sensitiveity of chronic pain: a patient controlled analgesia method. *Anaesthesia*. 1992;47:757-767.

[104] Bouckoms AJ, Masand P, Murray GB, Cassem EH, Stern TA, Tesar GE. Chronic nonmalignant pain treated with long-term oral narcotic analgesics. *Annals of Clinical Psychiatry*. 1992;4:185-192.

major depression, personality disorder, and other psychiatric conditions were most commonly associated with the development of abuse and dependence.

Jadad et al. utilized a double-blind randomized crossover design to examine analgesic relief obtained by the administration of morphine sulphate solution administered intravenously (10mg/ml and 30mg/ml).[105] Patients were administered either a 10mg/ml or 30mg/ml dose and controlled the rate of drug delivery. Pain relief was measured by VAS, VAS for pain intensity, pain relief measured with a categorical scale at regular intervals during an eight hour period, and baseline measurements with McGill pain questionnaire were obtained. The crossover dose was administered only when patients reported similar pain intensity as that at previous administration. A total of 13 patients were enrolled in the study and 10 completed both phases. On average, 230 mg of MS was utilized by patients. Although patients with neuropathic pain experienced their symptoms longer than those patients with nociceptive pain, no significant differences were observed in other characteristics such as pain intensity, age, McGill pain score, and the number of words utilized by patients to describe their pain. Pain response to the higher dose of morphine sulphate was superior and more side-effects were experienced with the lower dose (31 vs 36), however, this difference in adverse effects was not significant. Common side-effects experienced by subjects were drowsiness, itchiness, and concentration difficulties. It appears that both neuropathic and nociceptive pain are responsive to morphine; however, study results showed that patients with the latter type of pain achieved greater analgesic relief.

Tennant and colleagues published a report about 52 chronic non-malignant pain patients (mean age = 48.6 years) who were dependent on opioids and had been referred to the authors practice.[106] This group of patients had exhausted a variety of other pharmacological and non-pharmacological treatment options without much

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[105] Jadad AR, Carroll D, Glynn C, Moore RA, McQuay H. Morphine responsiveness of chronic pain: double blind randomized crossover study with patient controlled analgesia. *Lancet*. 1992;339:1367-1371.

[106] Tennant F, Robinson D, Sagherian A, Seecof R. Chronic opioid treatment of intractable, non-malignant pain. *NIDA Research Monograph*. 1988;81:174-180.

success. Most patients (92.3%) experienced pain of known etiology, which was musculoskeletal in nature. A majority of patients (88.5%) achieved adequate pain control, which was determined on the basis of patient self-reports and attending physician's clinical judgment. In this open label trial, pain was managed by either raising the original opioid dose, switching to a longer acting narcotic (methadone, oxycodone), combining low dose methadone with short-acting narcotic agents, or utilizing suppositories (hydromorphone/morphine). A wide variety of narcotic analgesics such as oxycodone, methadone, codeine, propoxyphene, hydromorphone, meperidine, and hydrocodone were utilized in this group of patients.

A report on the use of opioid analgesics in two separate patient groups with chronic pain of non-cancer origin concluded that patients experience adequate but incomplete pain relief without substantial improvement in functional status.[107] A majority of patients were treated with oxycodone (12/38), while other therapies included methadone, levorphanol, methadone/oxycodone, propoxyphe, propoxyphene/oxycodone, meperidine, codeine, pentazocine, pentazocine/propoxyphene, levorphanol/codeine. The report also suggested that patients undergoing long-term therapy might achieve better outcomes under the comprehensive supervision of one physician who assumes responsibility for management of these patients. Physician-patient relationship as a predictor of outcome with opioid therapy is an additional variable that is typically not evaluated.

A retrospective study of pain patients that had been stabilized on opioids showed satisfactory outcomes among compliant patients.[108] Noncompliant patients (n=18, 12%) were on less potent opioids (hydrocodone, codeine), displayed aberrant medication taking behavior, and reported limited pain relief. The rate of return to work improved in the compliant group.

A review of the safety and efficacy of Oxycontin concluded that although the drug is superior to placebo, it has no clinical advantages over immediate release

[107] Portenoy RK, Foley KM. Chronic use of opioid analgesics in non-malignant pain: report of 38 cases. *Pain.* 1986;25:171-186.
[108] Belgrade M, Chamberlain C, Kellar P, et al. Cited by: Belgrade MJ. Opioids for chronic nonmalignant pain. Choosing suitable candidates for long-term therapy. *Postgraduate Medicine*. 1999; 119-124.

oxycodone in the treatment of chronic non-malignant pain.[109] However, both formulations are superior to non steroidal anti-inflammatory drugs (NSAIDs) in this regard. In three of six studies reviewed, participants experienced fewer side-effect with the controlled release formulation, however, the authors concluded that SR oxycodone did not have a better side-effect profile than oxycodone. Except for one study that assessed postoperative pain, studies comparing oxycontin with other opioids were conducted in cancer patients. In five studies that compared oxycontin with sustained release morphine, no differences were found in either analgesic efficacy or adverse event profiles. The authors state that patients that have failed on a methadone trial received benefits from alternative opioid therapy suggesting that different narcotics, dosages, and dosage forms may produce different effects in any individual. This strengthens the case for individualized evaluations for selection of appropriate opioid therapy.

1.3.7.1 Summary of Studies Examining the Safety and Efficacy of Opioid Therapy in Chronic Non-Malignant Pain

This review indicates that regardless of the source of chronic pain, subgroups of patients with nociceptive, neuropathic, and osteoarthritis related pain obtain relief from the use of narcotic analgesics. Specific criteria that separate responders and partial responders from non-responders have not been clearly identified. Analgesic relief with opioid therapy is superior to that attained by NSAIDs. However, patients experience a greater number of side-effects with opioid therapy. Short-acting and long-acting analgesic therapies produce comparable analgesic relief. The evidence suggesting an improved side-effect profile with long-acting therapy is limited. However, patients have reported improvements in sleep, sleep quality, and mood with long-acting opioid therapy. Results from most of the studies examined suggested that patients tend to discontinue opioid therapy due to intolerable side-effects rather than lack of analgesia. Nausea, vomiting, itching, and drowsiness are some of the most

[109] Rischitelli DG, Karbowicz SH. Safety and efficacy of controlled-release oxycodone: A systematic literature review. *Pharmacotherapy*. 2002;22:898-904.

commonly reported adverse effects. Morphine doses upto 120 mg/day did not impair cognitive abilities of attention, memory, and concentration.[110] Central nervous system symptoms were commonly apparent among patients that did not respond to opioid therapy. Very few studies have reported improvements in functional status, participation in activities, or return to work among patients on opioid therapy. A tabulated summary of the studies reviewed is listed in Appendix A.

1.3.8 Mechanisms of Pain

A number of models have proposed mechanisms by which individuals experience pain. The biomedical model is limited and defines illness narrowly on the basis of biological, physical, and chemical attributes.[111] This model does not explain phenomena such as the presence of pain in the absence of pathology. Models that are based on the psychological perspectives claim that such phenomena can be attributed to various psychogenic factors including motivation (financial, family attention, etc) and reinforcement, wherein individuals may have become sensitized to painful stimuli long after factors causing pain (damaged tissue) may have resolved. Again, a disadvantage with the psychological perspective is the lack of an explanation for cases that are asymptomatic in the presence of obvious pathology. Individual variations in response to therapy, failure of surgical and pharmacological interventions, and "the low association between impairment and disability" indicate that a combination of factors ranging from biological findings to cultural norms and social interactions, and psychological functioning contribute to an individual's acceptance, response, and ability to cope with the condition.

[110] Moulin DE, Iezzi A, Amireh R, et al. Randomized trial of oral morphine for chronic non-cancer pain. *Lancet.* 1996;347:143-147.
[111] Turk DC, Flor H. Chronic pain: A biobehavioral perspective. In Gatchell RJ, Turk DCP, eds. Psychosocial factors in pain. Critical perspective. New York, NY:The Guliford Press. 1999.

1.3.8.1 The Gate Control Theory (GCT)

The GCT was proposed by Melzack and Wall in 1965 states that pain perception can be attributed to mechanical and psychological stimuli, and both factors play a role in altering response.[112] The GCT states that pain does not only involve sensory perceptions, but also includes affective and cognitive dimensions. The central nervous system plays a major role in the transmission and perception of pain suggesting that both psychological and somatic factors mediate pain. According to the theory, transmission of pain impulses to the brain occurs through the smaller afferent fibers that connect with large fibers in the dorsal horn of the spinal cord. The large fibers inhibit this transmission. If there is damage to large fibers, firing of slow impulses from the smaller fibers can lead to opening of the gate and perception of pain. Large fiber activity produces an opposite effect closing the hypothetical gate.

The spinothalamic and spinoreticular tracts constitute the ascending system and transmit sensory nociceptive information to the thalamus. The spinothalamic tract splits into the lateral branch and medial branch, which penetrate the brainstem reticular formation. The lateral branch "is responsible for the sensory discrimination of the spatial, temporal, and magnitude characteristics of pain, while the medial branch is associated with few painful stimuli."[113] The spinoreticular tract also splits into two branches that reintegrate in the periaqueductal grey (PAG) where heat and mechanical stimuli are perceived. Fibers that descend into the dorsal horn are believed to inhibit excitatory activity of impulses there. These fibers emerge primarily from the PAG and are capable of negating impulses that are generated by the afferent fibers. The PAG (located in the midbrain) is believed to inhibit transmission of pain impulses in the dorsal horn. The presence of enkephalin receptors in the PAG that bind with opioid like substances, stimulation of the PAG that causes release of

[112] Ibid.
[113] Skevington SM. Biological mechanisms of pain. In Newman S, Fitzpatrick R, et al. Psychology of Pain. John Wiley and Sons. Chichester, England. 1996. pp18.

enkephalins and endorphins with analgesic properties, and the inhibitory effects that opioid antagonists have on this stimulation corroborate the above finding.[114]

Numerous brain structures such as the frontal cortex, the PAG, and brain reticular formation play a role in cognitive and motivational-affective activities. Numerous emotions, fears, and avoidance-behaviors that arise in pain patients can be contributed to the involvement of these structures in the transmission and perception of pain. Prior to the GCT, pain research ignored the importance of cognitive processes, which were believed to occur secondary to pain. The complex processes involved in the perception of pain make it important to incorporate variables such as past experiences, attention, and cognitive activities and their association with therapy.[115]

The mechanism of pain as explained by the GCT provided a sound theoretical foundation and stimulated significant research resulting in major therapeutic advances in behavioral, cognitive, psychological, and medical strategies. Recent advances in technology have revealed some deficiencies in the GCT that have resulted in modifications to the theory. Despite these data, the GCT continues to serve as a heuristic basis for studying pain as it continues to provide a "powerful summary of the phenomena observed in the spinal cord and brain, and has the capacity to explain many of the most mysterious and puzzling problems encountered in the clinic."[116]

1.3.8.2 Neuromatrix Theory

Melzack, in 1999, proposed the neuromatrix theory, which incorporates theory of stress into the GCT. The important features of this neuromatrix include a network of nerve fibers, genetic factors that define the neuromatrix, and prior sensory stimulation and learned behaviors that are capable of sensitizing and modifying the neuromatrix.

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[114] Ibid.
[115] Turk DC, Flor H. Chronic pain: A biobehavioral perspective. Psychosocial factors in pain. Critical perspective. The Guliford Press. 1999; NY.
[116] Melzack and Wall, 1982. Quoted by: Turk DC, Monarch ES. Biopsychosocial perspective on chronic pain. In: Turk DC, Gatchel RJ (Eds.). Psychological approaches to pain management. The Guilford Press, 2002. New York, NY.

Collectively these factors are referred to as the "body-self neuromatrix." It is believed that the multidimensional nature of pain stems from these characteristics. Nerve impulses that are transmitted by the "neural network" are responsible for pain perception, and are generated in response to both peripheral nociceptive stimuli and central inputs that are independent of the former.117

Under normal physiological conditions, the human body does not experience any stress. Damage or injury to a tissue can cause stress and a disruption of normalcy triggering "neural," "hormonal," and "behavioral" mechanisms. Typically, the injury heals and the body returns to normalcy. However, stress that persists can compromise the "immune system and activate the limbic system." Chronic pain syndromes may often develop in response to chronic stress that causes deregulation.

Differences in stress levels, the manifestation of those effects, and the variability in perception of pain occur due to unique neuromatrix characteristics and experiences. Although pain is believed to occur secondary to stress, augmentation of this pain by other acute stressors prevents the body from achieving homeostasis. At the same time, pain itself, fear of pain, and concern about improvement contribute further to the abnormality, thereby perpetuating the cycle. Continuous nociceptive input can result in structural and functional modifications of the neuromatrix. CNS modifications may contribute to pain perception subsequent to healing of the original injury even in the absence of abnormal pathology.

1.3.9 Neuropsychological Functioning

"Cognition comprises the brain's powers to retrieve, process, store, integrate, and interpret information."[118] The 'stages of pain' model indicates that the latter two stages of pain, i.e., pain suffering and behavior contribute to impaired cognitive abilities in the chronic pain patient. Numerous studies have examined the effects of both chronic pain and experimental pain on cognitive functioning. Although not

[117] Ibid.
[118] Chapman SL, Byas-Smith MG, Reed BA. Effects of intermediate and long term use of opioids on cognition in patients with chronic pain. *The Clinical Journal of Pain*. 2002;18:583-590.

definitive, opioids tend to have an adverse effect on motor tasks, but do not significantly impair non-motor tasks that test memory and verbal skills. The following sections review the effects of pain (both chronic pain and experimental pain) on cognition and the effects of opioids on cognition among healthy and chronic pain patients.

In order to permit a better understanding of the empirical literature examining the association between experimental pain, chronic pain, opioid use and cognitive function, a description of the cognitive tests used most commonly in the literature are presented below:

1.3.10 Neuropsychological Tests Used to Assess Memory and Function Among Pain Patients

According to Posner and Boies, attention is composed of three distinguishable components: "(1) a readiness to respond called forth by a specific warning event; (2) selectivity, which involves the focusing aspect of attention; and (3) a limited processing capacity."[119] Although the primary goal of treatment for an individual experiencing pain is to obtain analgesia, the benefits of relief obtained through treatment must not be outweighed by intolerable side-effects.

The term vigilance has been used to describe sustained and focused attention (Lezak 1995). Successful completion of tasks involving vigilance is independent of age (≤80).

1.3.10.1 Attention Tests

1. Continuous Performance Test (CPT) – Rosvold et al., in 1956 originally developed the CPT as a measure of attention.[120] Test takers are required to press a key when presented with a "target letter" such as "X" or when some other letter is presented right before the target letter, e.g., when Z is presented before target letter X.

[119] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.
[120] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.

Various forms of the test have been developed that utilize both auditory or visual stimuli. Similarly, data can be collected as the number target stimuli missed or accounted for, reponse time to stimuli, etc. According to Spreen and Strauss, the Connors' CPT (1995) has been used extensively. The standardized test takes approximately 14 minutes to complete and individuals are required to respond by pressing a key for all letters except 'X'. Six blocks of testing must be completed with each block consisting of 20 subblocks with three different interstimulus levels. The computer software generates several results such as the number of "hits," "omissions," "commissions" (i.e., response frequency for unintended targets), "mean response time (RT) in milliseconds," "attentiveness (*d'*)" (i.e., ability to discriminate between targets and non-targets), "risk taking (ß)," "hit RT block change" (i.e., change in RT from one test interval to the next), "hit standard error (SE) block change" (i.e., standard error of change from one test interval to next), "hit RT interstimulus interval (ISI) change," "hit SE ISI change," and an overall index which is a weighted measure of all scores. One study found a direct relationship between IQ performance, academic achievement and CPT scores.

The test is associated with a variety of cognitive measures, for example, omissions correspond to deficits in sustained attention or vigilance while commissions correspond to impulsive behavior, lack of attention or memory deficits. Although the test provides a wide array of measures and is easily administered via a computer, reliability and validity data for Connor's CPT are not extensive. CPT scores have not been very useful to distinguish patients that may systematically differ with respect to various diagnostic criteria. The test can be ordered through Multi-Health Systems Inc at a cost of $495 (Canadian).

2. Paced Auditory Serial Addition Test (PASAT) – The PASAT is a measure of "information processing ability," and measures "sustained and divided attention."[121,122] Patients are presented a series of 61 random numbers that range from

[121] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.
[122] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.

one to nine. The objective of the test is to add pairs of numbers such that each number is added to the one immediately preceding it. A total of four trials can be completed and the rate of digit presentation increases gradually from 2.4 seconds in the first trial to 1.2 seconds in the last. Thus, a greater demand is placed on a subject's information processing capability with each trial. The test takes 15 to 20 minutes to complete if all four trials are included. Studies that have assessed the usefulness of the PASAT in brain injured individuals recommend it be used in high functioning patients compared to low functioning patients.[123]

Performance scores across different trials are highly reliable (Cronbach's alpha = 0.9). For tests that are conducted within short time intervals, test retest correlations are ≥ 0.9. There is a substantial body of evidence documenting the construct validity of the test. If the proportion of errors exceeds 20 percent, the interpretation of this test as a measure of attention is compromised. Practice effects have been noted, particularly if successive tests are administered within a week from each other. Test tape along with scoring instruction is available from Neuropsychology Laboratory, University of Victoria, P.O. Box 1700, Victoria, BC BC V8W 2Y2, Canada at a cost $50 (Can), while The Psychological Corporation, San Antonio, TX-78204 offers a computerized version for $716.50 (US). The PASAT is capable of detecting very subtle impairments in information processing ability, but the sensitivity of this test does not come without cost. "Patients perceive this sensitive test as very stressful: most persons – whether cognitively intact or impaired – feel under great pressure and that they are failing, even when doing well.[124]" Thus, it is necessary to forewarn the patients about the demanding nature of the test.

3. Symbol Digit Modalities Test – The test is a measure of visual scanning and tracking aspects of attention, and motor speed. Patients are presented with several geometric designs from which they are required to identify symbols, and substitute

[123] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.

[124] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. pp 373.

each symbol with a corresponding number. Oral and written versions of the test are available. A total of 5 minutes are required for the test. It has been reported that frequent administration (eight test sessions at 2 to 4 week intervals) may result in practice effects; however, minimal effects have been observed with substantial gaps between subsequent tests. Regardless of interval, test-retest correlations have ranged from 0.72 to 0.80. Patient groups such as substance abusers, older adults that are sedentary, aging individuals, and those with head injuries have performed poorly on the test indicating impairment. The SDMT is highly correlated with the Wechsler Digit Symbol Test (r = 0.62 to 0.91), and also captures aspects of performance measured by the Trail Making and choice reaction time tests. Spreen and Strauss advocate caution with the use of this test among litigating patients. The test kit is available at a cost of $60 (US).

4. Visual Search and Attention Test (VSAT) – This test measures ability to maintain sustained attention and visually track targets/stimuli. A total of four trials must be completed. In the first two practice trials, subjects are presented with an arbitrary target, "letter" or "symbol" that must be crossed out. In the test trials, patients are presented with a variety of symbols and letters in blue, red, and green ink. The objective is to identify all the Hs and slashes in blue ink. Each trial must be completed in 60 seconds. A total of about 6 minutes are required to complete test administration. Scores are calculated by adding the number of correct hits in the allotted time. "Percentile scores are used to interpret a patient's performance on the VSAT."[125] The VSAT has low to moderate correlations with the PASAT (0.30) and Digit symbol test (0.65) indicating that it may not be a very effective tool to measure attention. Psychological Assessment Resources provides the test at a cost of $58 (US).

5. Digit Span Subtest of the Wechsler Adult Intelligence Scale–III (WAIS-III) – The

[125] Ibid.

tests comprises two parts, Digits forwards and backwards, and is a measure of span of short term recall. The test consists of seven pairs of random numbers.[126] In the digits forward test, subjects are required to repeat the numbers in the same sequence as the examiner. The procedure is followed until the patient fails to repeat correctly or successfully repeats a nine digit series of numbers. Average raw score in the normal population is 6 (+/- 1). Patients that score 5 or above are considered to have a normal span of attention, a span of 4 is indicative of borderline impairment, and a span of 3 indicates impairment.[127] The test primarily measures "efficiency of attention" also referred to as "freedom from distractability."

In the digits backward test, the number sequences can range from two to eight digits. Subjects repeat the sequence in the exact reverse order until failure or entire sequence is recalled correctly. A digit span of 4 and above is considered to be within normal limits, a span of 3 suggests some deficiency, and a span of 2 is indicative of a defect (upto age 60). The digit backwards scores vary with education and age. An average decline of 1-point below the normal may be expected for individuals above age 70. "The ability to reverse digits, or to spell a word or recite a letter sequence backwards, is probably characteristic of normal cognitive function and language processes related to the brain's normal function of temporal ordering."[128]

The digits forward and backward tests should preferably be scored separately. A suboptimal performance on the digit backward test is more than likely an indication of impaired cognitive function. Patients that perform poorly on the backward test may perform well on the digits forward test. Thus, combining results from the two tests may lead to an inaccurate conclusion. "For example, a total score of 11 may be assumed to be normal, however a digits forward score of '8' and a digits backward score of '3' (total = 11) would be rarely observed in the normal population."[129] The reliability coefficients obtained from subsequent tests are high (range = 0.66 to 0.89)

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[126] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.

[127] Ibid

[128] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.

[129] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1995.

with few practice effects. An individual that correctly repeats eight and seven digits on the digits forward and backward test respectively is assumed to lie within the normal distribution, and thus prolonged testing may not be necessary.

6. Digit Symbol Test of the WAIS-III – The test is similar to the digit symbol substitution test described above. The test comprises a series of boxes labeled with random numbers ranging from one to nine, along with nine symbols that are also identified by numbers. The subject's task is to substitute the appropriate symbol for each corresponding number.[130] The digit symbol test is a measure of ability to focus and maintain visual attention. Individuals with motor difficulties or with impaired motor function tend to perform poorly on this test. The test does not draw upon an individual's intelligence, memory or learning ability. The digit symbol does tap the following resources: motor persistence, sustained attention, response speed, and visuomotor coordination. The test is reliable, which is evident from the high test-retest reliability (range 0.82 to 0.88). Practice effects are negligible. The digits symbol test is highly sensitive and "failures on this test may be the result of different factors or their interplay, or of a sore shoulder, or stiff fingers." (Lezak 1995) Age (greater than 60), gender (being male), and a lower education level are all associated with underachievement on the test.

1.3.10.2 Visual, Visuomotor, and Auditory Tests

1. Trail Making Test (TMT) – This test is also referred to as the Partington Pathways, can alternatively be administered as the Oral Trailmaking Test, Color Trails Test (CLT). The tests are a measure of "speed of attention," "sequencing," "mental flexibility," and "visual search and motor function."[131] The Oral Trailmaking Test does not assess the lattermost cognitive function. The test is composed of two parts; in Part A, subjects are required to connect 25 circles that

[130] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.
[131] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.

enclose numbers located randomly on a page in a specified order. In Part B, the 25 circles contain either numbers or letters that must be connected alternatively. Retests can be conducted by altering the sequence to minimize practice effects. The CLT is designed to minimize language barriers associated with the TMT. The circles are shaded as pink or yellow. In Part 1, odd-numbers are assigned a pink shade and even numbers are shaded yellow, and subjects must alternate between colors. In Part 2, numbers from 1 to 25 are presented two times with one series shaded pink and the other yellow. "Subject is required to connect the numbers from 1 to 25 alternating between pink and yellow circles and disregarding the numbers in circles of alternate color."

An average of five to ten minutes is required to complete test administration. A ratio of the two test scores can also be computed. Scoring for the TMT has evolved over the years.[132] A 10-point scale which accounted for the amount of time taken to complete the test was used. A patient who made three errors was instructed to stop working on the test. Now, a patient who makes an error is instructed about the error and asked to correct it. Performance scores are measured as the amount of time required to complete both parts of the test. Although the errors are accounted by the amount of time required to make corrections, the reliability of the test is compromised since the rate at which corrections are pointed out and made is a function of the examiner. Interrater reliability is at least 0.9 for both parts of the test. Lezak reported reliabilites measured as the coefficient of concordance for parts A and B of the test to be 0.78 and 0.67 respectively on repeated administrations. The interpretation of performance scores must take a patient's age into account. A correlation of 0.49 between Part A and B of the TMT has been reported, indicating that the tests measure different aspects of cognitive function.

2. Clock Drawing Test – The test has been used as a tool to screen for dementia. Involves either free hand drawing or utilizes worksheets with circles that are printed. The circle serves as a clockface and subjects are required to draw the clock hands

[132] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.

corresponding to the time. A total of 5 minutes are required for the test. A standardized scoring system is available. This test has been used most commonly in patients with Alzheimer's disease, since it is very easy to administer. The test has been shown to accurately discriminate between healthy older adults, Alzheimer's patients, and those with dementia and depression.

1.3.10.3 Language Tests

1. Controlled Oral Word Association Test – This test is also known as the FAS as it employs three letters F, A, and S, to test patients' verbal fluency.[133] The patient is required to list without repetition as many words for each letter during a one-minute interval. Proper nouns, numbers, and same words with different suffix endings are not allowed. The frequency of words in a dictionary with the letters F, A, and S, increases sequentially. In order to assess semantic association, patients are asked to name things from a category after being presented with an example such as cat for the category of animals. Foods, grocery items, etc. are examples of other categories.[134] Patients are ranked on the basis of a percentile score that is age, gender, and education adjusted. The interrater reliabilities are very high and test-retest reliability has ranged from 0.65 to 0.88 in adults.

1.3.10.4 Memory Tests

1. Rey-Osterrieth Complex Figure Test (CFT) – The purpose of this test is to assess visual memory and ability to reconstruct complex figures.[135] Motor skills of subjects are also assessed. Participants are presented with a diagram and are required to produce a copy of the image, and subsequently asked to draw the figure from memory. Subjects may be asked to recall the figure either immediately or after 3 minutes, and sometimes even longer time intervals. It has been observed that few

[133] Ibid
[134] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.
[135] Ibid

differences exist between shortened and delayed testing for normal subjects, since most memory loss occurs within the first few minutes. If such a difference does occur, it is interpreted t have clinical significance. This is true provided the delayed recalls are less than an hour. A total of 10-15 minutes are required to complete test administration. Each component of the figure is assigned a total point-value, and scores are assigned based on completeness, accuracy, distortion, etc. When considering multiple raters, reliability scores have been reported as 0.8 or greater. The reliabilities for the various components have ranged from 0.14 to 0.96.

2. California Verbal Learning Test (CVLT) – The purpose of the test is to gauge an understanding of techniques utilized to learn verbal material. Additionally, the test is a good measure of the amount of verbal material that can be retained. The test is administered over several trials. Patients are presented with a shopping list containing 16 items (Includes a total of 4 categories each containing 4 items). Subjects are then presented an alternate list (2 categories are the same as above and 2 are different) that serves as a distraction. Participants are then subjected to an immediate and a 20-minute delayed recall of the first list. The test takes approximately 35 minutes to complete. Alternate short forms containing nine items have also been developed for use among memory-impaired older adults. The CVLT has been shown to be internally consistent, and correlation scores for the various administrations have not been consistent ranging from 0.12 to 0.79. Interrater reliability is questionable.

1.3.10.5 Executive Functions and Motor Performance Tests

1. Stroop Test – The Stroop test is a measure of ability to refocus attention and to respond in a manner that is atypical or deviates from the norm.[136] The test has four trials and consists of three cards with information presented on them. In the first trial, paticipants are asked to read a card containing color names (blue, green, etc) printed in black ink. In task two, participants are required to read color names on a card

[136] Ibid

printed in colored ink. In task 3, a card with boxes in various colors is presented and the participant identifies the color. Trial four is similar to trial two except that participants must read the color of the print. Administration of the test requires about five minutes. Different parts of the test and subsequent test scores have showed high reliability (0.75 and greater). Performance on this test is related to that on the Digit symbol, digit span, and block design test, and is measured as the amount of time required to name the colors. Depressed and anxious patients have an impaired performance on the Stroop test. The test is not useful in a sample of patients that is visually impaired.

2. Finger Tapping Test (FTT) – This is a test of manual dexterity, and was also referred to as the Finger Oscillation Test.[137] Subjects are simply asked to tap their index finger as fast as they can while keeping their palms flat against a pad. The tapping speed for both the preferred and non-preferred hands is measured. Alcoholics, head-injury patients, and those in the early stages of dementia have performed poorly on the FTT. In addition to motor function, "the speed, coordination, and pacing requirements" of the test can vary with "level of alertness, impaired ability to focus attention, or slowness of responses."

3. Purdue Pegboard Test – The pegboard test also measures manual dexterity. The board consists of 2 sets of 25 grooves that run along the length of the board.[138] Subjects are required to place pins that are located at the top of the board in the groove. The test consists of three trials requiring placement with preferred hand, non-preferred hand, and both hands within a 30 second time limit. Performance is measured as the number of pins successfully place. An additional fourth trial involves placing a pin, a washer, a collar, and another washer in order alternately with both hands. A one-minute time limit is set for this test.

One to two week retest reliabilities have been reported in the range of 0.63 to 0.82. Average scores for groups such as production workers and those seeking

[137] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.
[138] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New York. 1998.

production jobs have ranged from 15-19, 14.5-18, and 12-15.5 for right, left, and both hands respectively.[139]

4. Grooved Pegboard Test – This test is more difficult than the Purdue test, as it utilizes a smaller board with grooves arranged in different directions. The pegs are designed so that they have to be rotated to fit the groove correctly, thus making it a more sensitive measure of motor function.[140]

5. Block Design Test of the WAIS –R – The test involves construction using blocks and tests visuospatial as well as motor capabilities. Numerous patterns can be used to increase the level of task difficulty. The time limit must be competed in either 1 or 2 minutes depending on whether 4 blocks or 9 blocks, respectively are required in the construction. Older individuals tend to perform the task more slowly. Educations does not influence ability to construct designs. Split half reliabilities range from 0.82 to 0.89, while test retest reliability coefficients ranged fro 0.73 (in older adults, mean age - 79±3.5) to 0.84.

6. Hopkins Verbal Learning Test (HVLT) – The test consists of six lists, each list comprised of four semantically similar words in groups of three for a total of 12 words. Subjects are allowed to practice (3 trials) and then must identify 24 words with 12 words directly from the list, 6 others are associated with the original 12 and the last six are have no connection.[141]

7. North American Adult Reading Test - This is a test of verbal ability. Subjects are simply required to read a list of words that must be pronounced correctly. The NAART is a test of assessing an individuals education level. The underlying assumption of the test is that ability to read words is reflective of reading ability. This is not a commonly used test in neuropsychology.[142]

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[139] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1983.
[140] Ibid
[141] Lezak MD. Neuropsychological assessment. Oxford University Press. New York. 1995
[142] Ibid.

Table 1.2 Summary of Commonly Used Cognitive Tests in Literature Review

TEST	TIME (MINS)	SINGLE COMPOSITE MEASURE	ASPECT OF COGNITIVE FUNCTION	RELIABILITY DATA
CPT	14	Multiple measures: # of hits, omissions, commisions	Vigilance, sustained attention, memory deficits.	Few studies have assessed reliability and validity
PASAT	15-20	correct responses for each test series or mean score	Sustained attention & information processing.	Cronbach's $\alpha = 0.9$
SDMT	5	Time for completion	Visual scanning & tracking, motor speed.	Test-retest corr – 0.72 to 0.80
VSAT	6	# of correct hits	Attention & visual tracking	May not be a good measure of attention
DSTF	2-3	Average raw score	Immediate recall	Reliability coeff – 0.66 to 0.89
DSTB	2-3	Average raw score	Temporal ordering	Reliability coeff – 0.66 to 0.89
DSYT	1.5	# of correct responses	Motor persistence, sustained attention, speed, and visuomotor coordination	Test-retest reliabilities (range 0.82 to 0.88)
TM A&B	5-10	Time required to complete test	Attention , mental flexibility, visual search, and motor function	Correlation between A&B – 0.49
CDT	5	Standardized scoring system	Distinguishes between healthy controls, dementia, and alzheimer's patients	

Table 1.2 (Continued) Summary of Commonly Used Cognitive Tests in Literature Review

COWA	One/ letter	# of words	Verbal fluency Psychomotor function	Test-retest reliability - 0.65 to 0.88
RO-CFT	10-15	completeness, accuracy, distortion.	Visual memory	Reliabilities – 0.14-0.96
CVLT	35	Numerous measures based on subtests	Verbal memory	Inter-rater reliability questionable.
ST	5	Amount of time required to name colors	Ability to refocus attention	High reliability among sub-parts (≥ 0.75)
FTT	3-4	Tapping speed dominant and non-dominant hand	Test of manual dexterity	
PGP	2	# of pins correctly placed	Manual Dexterity and motor performance	Test-retest reliability - 0.63 to 0.82

CPT – Continuous Performance Test PASAT – Paced Auditory Serial Attention Test, SDMT – Symbol Digit Modalities Test, VSAT - Visual Search and Attention Test DSTF – Digits Span Test Forwards, DSTB – Digits Span Test Backwards, DSYT – Digit Symbol Test, TM A&B – Trail Making Test Part A&B CDT – Clock Drawing Test, COWA – Controlled Oral Word Association Test, RO-CFT – Rey Osterrieth-Complex Figure Test, CVLT – California Verbal Learning Test, ST – Stroop Test, FTT – Finger Tapping Test, PGP – Purdue/Grooved Pegboard Test

Crombez, Eccleston and colleagues have argued that studies assessing the effects of various external stimuli (distractions) on pain perception have neglected the attentional deficits that pain itself can produce.[143] In addition to disrupting normal day-to-day activities, pain can interfere with a variety of tasks that require concentration by drawing attention away from them. Individuals experiencing pain bear an opportunity cost as their ability to focus attention on other tasks that require attention maybe compromised. Such a conceptualization of pain offers an opportunity for the validation of data on pain-related attention and memory deficits obtained through self-reports and neuropsychological tests. Numerous behavioral and activity measures can also be used to assess the interruptive nature of pain. Subsequent sections of this chapter are devoted to the effects of pain and opioids on cognitive impairment.

1.3.11 Cognitive—Affective Model of the Interruptive Function of Pain

Attention can be defined as an individual's capability to focus on multiple tasks. As the attention required by these multiple tasks exceeds a certain threshold, performance can diminish, cease, or become impaired.[144] The pain literature does not offer a theoretical understanding of the manner in which pain can divert attention from other tasks, despite recognition that pain perception and behavior incorporate mechanisms of attention. Human behaviors are driven by goals, and often these behaviors can be interrupted by insufficient information or other more important priorities. It has been argued that attentional systems must be capable of responding to dangerous or novel situations as well. Pain is one example of a danger that would trigger interruption of other tasks, as protecting the body from harm is recognized as a basic goal atop the hierarchy of all needs.

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[143] Crombez G, Eccleston C, Baeyens F, Eelen P. The disruptive nature of pain: An experimental investigation. *Behaviour Research and Therapy*. 1996;34:911-918.
[144] Eccleston C, Crombez G. Pain demands attention: A cognitive—affective model of the interruptive function of pain. *Psychological bulletin*. 1999;125:356-366.

In 1971, Walker concluded that students subjected to electrocutaneous stimuli found it difficult to focus on an attentionally demanding task. Numerous studies have corroborated this finding. Expectation of pain can also cause emotional distress. Pain is perceived as a threat and greater the threat potential of a stimulus, more likely is the possibility of task interruption.[145]

Several studies have tested distraction strategies that can be used to draw attention away from pain. Low intensity rather than high intensity pain tended to respond to these strategies. Distraction stimuli that were qualitatively similar to pain producing stimuli were no more effective than dissimilar distractions. Distraction strategies with positive or pleasant emotional content were more successful at increasing pain threshold and tolerance as compared to anger or other unpleasant emotional content. [146]

In the context of chronic pain, interruption is often expressed as somatization, higher utilization, depressive symptomology, and withdrawal from activity and social interactions. Interruption according to this model may be a mechanism to escape from pain and pain producing stimuli rather than a pathological response to pain.[147] "Pain patients often report being unable to read, watch television or complete a simple task because of their inability to attend to the material or activity."[148] This lack of concentration also affects a pain patient's ability to complete work-related responsibilities effectively. Patients involved in jobs that are physically demanding find it extremely difficult to maintain employment. They are advised to refrain from physically demanding tasks, and the inability to concentrate makes it challenging to train for jobs that require greater mental ability, thus making it difficult to find a new vocation

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[145] Ibid.
[146] Ibid.
[147] Ibid.
[148] Jamison RN, Brocco TS, Parris WC. The influence of problems with concentration and memory on emotional distress and daily activities in chronic pain patients. *International Journal of Psychiatry in Medicine*. 1988;18:183-191.

1.3.12 Cognitive Function in Chronic Pain Patients

In one of the earliest studies to examine memory and concentration problems in pain patients, Jamison and colleagues collected information on a variety of measures such as the Symptom Checklist-90-R (SCL-90-R) and pain evaluation questionnaire.[149] A five point rating scale (1 – not at all and 5-extremely) was used to assess the extent to which a patient felt depressed, anxious, or irritable. Memory and concentration problems were assessed through two items rated on a 5-point scale on the SCL-90-R: 1) "how much are you bothered by trouble concentrating?' and 2) how much are you bothered by trouble remembering things?"

Patients with a score of 2 or greater on these items (reflecting moderate to extreme concentration problems) were classified as one group (n = 198). The group with no concentration and memory problems (n = 195) did not differ from the former on demographic variables such as age, gender, and marital status, or on intensity and duration of pain. Patients with concentration troubles provided significantly higher ratings for depression, anxiety and irritability, reported a significantly greater number of conflicts within the home and experienced pain that worsened while sitting. Fewer patients with memory troubles were satisfied with social activities (23.3% vs 35.1%, $p < 0.01$) and sexual activities (26.8% vs 47.2%, $p < 0.001$). Except for work and shopping, patients with memory troubles reported a significantly greater interference in socializing, hobbies, exercise, sleeping, and sexual activities due to pain. Only 30 percent of the sampled patients were working, and this may have accounted for the lack of difference between the two groups with regard to work. Pain patients are prone to complaining about cognitive deficits and the use of subjective reports may be a limitation. Additionally, a global question about concentration and memory deficits provides little information about the extent and nature to which patients are affected. The measures used in this study were not substantially validated and lacked suitable psychometric properties.

[149] Ibid

Dufton utilized the Cognitive Failures Questionnaire (CFQ) to assess everyday cognitive skills of attention, perception, memory, and motor functioning.[150] A total 157 patients who had experienced pain for an average duration of 5.7 years completed the CFQ and BDI. A median split on the CFQ score was used to create two groups, group 1 (n = 79) with an average score of 26.1, and group 2 (n =78) with an average score of 49.1 indicating a high level of cognitive inefficiency. The groups did not differ significantly on pain descriptors, chronic nature of pain, prescription and OTC drugs, and a variety of daily activities (group 2 indicated that participation in daily activities was less desirable). However, the high CFQ group scored significantly higher on the BDI (mean = 13.8) compared to the low CFQ group (mean = 8.6), the former score being indicative of mild depression. These results do not elucidate the relationship between pain, cognitive inefficiency, and affective distress. Pain patients are believed to experience a mild form of cognitive dysfunction and self-report measures utilized by Dufton and Jamison may not be sensitive enough to detect such impairment.

Kewman et al. administered the Neurobehavioral Cognitive Status Examination (NCSE) to 73 patients with musculoskeletal pain.[151] The NCSE includes items that evaluate orientation, attention, language, functioning, visuospatial constructional abilities, memory, arithmetic calculation, and reasoning. A total of 23 participants (32%) performed poorly with deficits observed most commonly in the following domains: attention (n = 3); memory (n = 13); calculation (n = 6); and test of similarity (n = 8). Pain intensity ($r = -0.475$, $p < 0.001$) and interference in daily activities ($r = -0.304$, $p < 0.001$) were significantly correlated with NCSE scores. The relationship was not significant when emotional distress was added as a control variable, indicating that affective distress modifies the relationship. The relationship between duration of pain and cognitive dysfunction approached significance, and higher education was associated with lower cognitive dysfunction. It is argued that well

[150] Dufton BD. Cognitive failure and chronic pain. *International Journal of Psychiatry in Medicine.* 1989;19:291-297.
[151] Kewman DG, Vaishampayan N, Zald D, Han B. Cognitive impairment in musculoskeletal patients. *International Journal of Psychiatry in Medicine*. 1991;21:253-262.

educated patients may be able to compensate for cognitive difficulties, thus leading to underestimations about the prevalence of neuropsychological impairment in these populations.

Schwartz and colleagues developed a battery of screening tests to assess cognitive impairment in chronic pain patients designed to minimize screening costs and time.[152] The battery consisted of the Trails Part A & B, the controlled word association (CWA) test, and the paced auditory serial addition test (PASAT). Results from the study showed that patients with chronic pain and history of trauma performed poorly on cognitive screening tests than pain patients without trauma. These differences were not significant, but a global impairment rating showed significant differences between the trauma (18 of 25) and non-trauma (4 of 17) patients. The deficits are often subtle and therefore may not be detected, however, even these less than obvious deficits can affect activities that require attention and concentration. Subsequent evaluation indicated that results from the battery correlated perfectly with comprehensive neuropsychological assessment tools. Heyer et al. evaluated the effect of pain on neuropsychological tests among patients that underwent spine surgery.[153] A battery of tests designed to assess neuropsychological function were administered before surgery and one day post surgery. The Trails Part A & B (measure visuomotor tracking and complex attention), Controlled Oral Word Association test (COWA), and the Rey Complex Figure were administered as they represented a broad assessment of cognitive function. A standardized numeric 11-point pain intensity rating scale was also administered (0- no pain and 10 – worst possible pain). Post-operative pain correlated with test scores on the Rey Complex figure ($r = -0.577$, $p = 0.004$) and Trails A test ($r = 0.527$, $p = 0.01$). Patients treated with centrally acting analgesics (Percocet and Morphine) post-operatively performed poorly on the COWA and Rey Complex Figure tests. Results from this study suggest

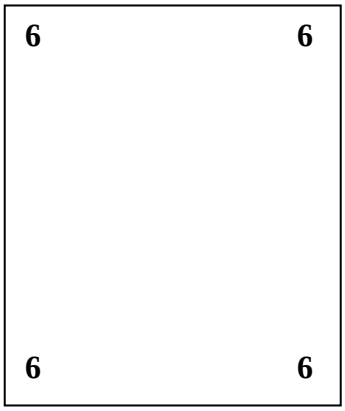
[152] Schwartz DP, Bath JT, Dane JR, Drenan SE, Degood DE, Rowlingson JC. Cognitive deficits in chronic pain patients with and without history of head/neck injury: development of a screening battery. *The Clinical Journal of Pain*. 1987;3:94-101.
[153] Heyer EJ, Sharma R, Winfree CJ. Severe pain confounds neuropsychological test performance. *Journal of Clinical and Experimental Neuropsychology*. 2000;22:633-639.

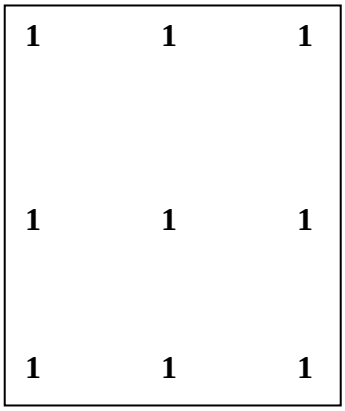
that although chronic pain may not be associated with neuropsychological functioning, acute pain does show an association. However, results from other studies have indicated otherwise. Effects of anesthesia and trauma due to surgery were not controlled.

Eccleston conducted a series of three studies to assess the association between pain and attention. Attention was assessed as a measure of time required to respond to information presented in the form of cards on a computer screen. These cards resemble playing cards on which numbers ranging from one to nine are printed in regular pattern (Arabic numerals). The cards were identified on the basis of the digit value V (i.e., six and one for the cards shown below) or the number of digits N (i.e., four and nine for the cards shown below) printed on the card.[154] In experiment one, participants (chronic pain patients, n = 20; controls, n =10) identified the numerical value (V) of the card (dominant information) followed by the number of digits (N) printed on the card (non-dominant information). The amount of time needed for responding to non-dominant information usually increases. The amount of time required to complete the task was much higher with the use of non-dominant information for both pain patients and controls. It was concluded that persistent pain did not draw attention away from such a basic task. It was further hypothesized that performance on a complex task would be impaired due to pain. In experiment two, pairs of cards placed adjacent to each other were presented and subjects were asked to identify the card with larger values in one trial and larger number of digits in the second trial.

[154] Eccleston C. Chronic pain and attention: a cognitive approach. *British Journal of Clinical Psychology*. 1994;22:535-547.

Figure 1.2 Cards Presenting Dominant and Non-Dominant Information





An example of the stimuli used in experiment 2 in the Eccleston

Amount of time required to complete the task was used as the dependent measure. A 3x2x2 analysis of variance model [pain (3 categories) by task (2 categories) by difficultly (2 categories)] was used. Although main effects for all variables were significant, an interaction between pain levels and task was significant [$F(2,33) = 13.25$, $p < 0.01$). Patients with high intensity pain required the most time to complete the non-dominant task, i.e., time required to call the N printed on the cards. Chronic pain patients that reported high pain intensity on the VAS and numerical rating scale required a significantly greater amount of time to complete the recognition task than controls ($p < 0.05$) and those reporting low intensity pain ($p < 0.05$).[155]

In the second study of this series, Eccleston hypothesized that patients experiencing low intensity chronic pain are capable of switching attention back and forth between pain and task to be completed. There is some degree of interference due to the pain, however, the duration and intensity is not large enough to systematically influence performance on the task. The same procedure utilized for

[155] Ibid.

experiment two in the previous study (Eccleston, 1994) was utilized in experiment one for this study.[156] The non-dominant task is a test that requires attention processing that is similar to that of pain processing. Results from a two-way ANOVA (pain X task) showed a significant interaction between the independent variables. Patients reporting high intensity pain took significantly ($p < 0.05$) more time for the recognition task (non-dominant information) than controls and low intensity pain patients (median VAS ≤ 39.6 range 1- 75; median numerical rating scale ≤ 66, range 1-80). Patients experiencing low intensity pain may be able to temporarily shift their attention to focus on the task at hand such as a test; scores on these tests do not reflect a substantial effect of low-intensity pain on cognitive function.

A competing hypothesis, namely, that these patients are experiencing psychoanalgesia at the time of task completions was suggested. However, this suggestion cannot be empirically tested. In order to test the ability to switch theory, the experiment was modified by alternating between presentation of non-dominating and dominating information rapidly, without any cues. This test was modified on the premise that the need to focus on two distinct tasks requiring attention that arise from the same stimuli places a greater burden on an individual's ability to concentrate. Thus, it was hypothesized that if patients with low intensity pain did refocus their attention, such a demanding task would hamper their reaction time. The results showed that patients with low intensity pain did not differ significantly from the control group lending support to the theory that these patients experienced distractional psychoanalgesia. In conclusion, patients experiencing high intensity pain perform poorly on task requiring central attention as compared to low intensity pain patients or controls.

Eccleston et al. hypothesized that patients with high intensity chronic pain and high somatic awareness (greater number of health complaints in addition to pain)

[156] Eccleston C. Chronic pain and distraction: An experimental investigation into the role of sustained and shifting attention in the processing of chronic persistent pain. *Behavior Research and Therapy*. 1995;33:391-405.

were more likely to experience attention difficulties.[157] Attention was assessed as a function of response time required to process dominant and non-dominant information as described above. The results showed that patients with high intensity pain (n = 16, mean on VAS (100mm) = 60.5, sd = 12.9) and high somatic scores as obtained on the Modified Somatic Perceptions Questionnaire (MSPQ) experienced greater attention deficiencies than high intensity/low somatic (n =5), low intensity/high somatic (n =8), and low intensity/low somatic (n = 17) patient groups. These patients also experienced greater affective distress evidenced through significantly higher scores on the Zung Depression Scale {$t(22) = 1.92$, $p < 0.04$} and the Hospital and Anxiety Depression Scale *Depression*: {$t(22) = 1.83$, $p < 0.04$} and *Anxiety* {$t(22) = 2.19$, $p < 0.02$}. A large proportion of the sample utilized medications such benzodiazepines, opioids, and antidepressants. Medication use was not associated with task performance. High intensity/low somatic awareness group patients reported significantly [$t(19) = -1.547$, $p = 0.07$] higher pain intensities (mean = 68.0) than the high intensity/high somatic awareness group patients (mean = 58.1). Results from this study indicated that somatization, depression and other affect variables are associated with processes of attention.

Schnurr and McDonald examined memory difficulties in back and neck pain patients who were injured in vehicular accidents (n = 56) or at work (n = 27).[158] Patients that utilized psychotherapy services (n = 20) and general medical and dental patients (n = 24) served as controls. The pain patients scored significantly higher on the Beck Depression Inventory (BDI) and [$F(3,123) = 32.32$, $p < 0.0001$] and the State-Trait Anxiety Inventory [$f(3,123) = 22.90$, $p < 0.0001$] indicating higher levels of depression and anxiety than control groups. Average ratings on all three subscales of the Memory Observation Questionnaire-2 scales indicated that pain patients experienced significantly greater memory problems than the medical and dental controls. Although average self-reported memory ratings for all pain patients were

[157] Eccleston C, Crombez G, Aldrich S, Stannard C. Attention and somatic awareness in chronic pain. *Pain*. 1997;72:209-215.
[158] Schnurr RF, MacDonald MR. Memory complaints in chronic pain. *Clinical Journal of Pain*. 1995;11:103-111.

lower than psychotherapy patients, these differences were not significant for all sub-tests. An analysis of covariance (ANCOVA) indicated that pain and control groups did not differ significantly on this measure after controlling for depression and anxiety. Of the two covariates, depression significantly correlated with self-reported memory functioning. However, ANCOVA results showed that average scores on the Chronic Pain Memory Complain Questionnaire (CPMCQ) between pain and control groups differed significantly [$F(3,119) = 3.44$, $p = 0.019$] despite partialling out the effects of depression and anxiety. Since no significant differences were observed between the two pain patient groups the authors believed that " mild head injury would not appear to be the sole contributing factor to memory complaints in chronic pain patients.[159]" Self –reported use of codeine and psychotropic drug use were not associated with memory problems.

Patients with persistent pain may code and recall information differently from healthy controls. Studies evaluating recall bias in depressed patients and controls showed that the former tend to recall depressed words (used in a self-reference context) more easily than non-depressed words. Pincus et al. hypothesized that chronic pain patients with pain-associated experiences and memories may be subject to a similar recall bias when presented with information containing pain stimuli.[160] The results from this study indicated that control subjects recall more information than pain sufferers {$F(1,40) = 6.99$, $p = 0.01$). Pain patients, however, recall significantly more sensory pain information in reference to themselves than in reference to others and recall more neutral (everyday use words) information that is presented in reference to others. Pincus and colleagues replicated these findings in another study and concluded that anxiety and depression did not influence this recall bias.[161] However, the results also showed that words indicating painful stimuli do not draw attention away from pain patients and they perform similar to controls when

[159] Ibid
[160] Pincus T, Pearce S, McClelland A, Turner-Stokes L. Self-referential selective memory in pain patients. *British Journal of Clinical Psychology*. 1993;32:365-374.
[161] Pincus T, Fraser L, Pearce S. Do chronic pain patients 'Stroop' on pain stimuli? *British Journal of Clinical Psychology.* 1998;37:49-58.

emotional distress is included as a control variable. The authors concluded that pain draws greater resources from activities that require effortful processing rather than automatic processing.

Assignments that involve automatic processing consume minimal resources of the brain and those that require effortful processing place a considerable strain on attention capacity.[162] Automatic processes tend to occur at a subconscious level, do not draw on other cognitive resources, and can be characterized as occurring involuntarily. Elaborative or effortful processes on the other hand draw on various mechanisms and resources that may be utilized for other mental activity, are critical for grasping knowledge, and are often voluntary. Similarly, it has been suggested that pain hampers explicit memory, which is measured by using free recall techniques to a greater extent than implicit memory, which is measured using cueing techniques.

Townsend evaluated the effects of chronic pain on processing, memory, verbal functions (i.e., reading, writing, verbal memory, and temporal relationships), and nonverbal processing such as visuospatial information.[163] Participants (n = 65) with a confirmed diagnosis of arthritis were enrolled and average age was 50.9 (s.d.= 13.3) years. Patients reported high pain intensity (mean = 7.8, s.d. = 4.9) and fatigue (mean = 9.7, s.d. = 4.8) levels measured on a 10 cm VAS. Patients had not utilized any opioid analgesics in the 24 hours prior to administration of tests. The following neuropsychological testing instruments were administered: The North American Adult Reading Test (NAART); the Mood Assessment Scale (MAS); PASAT; the Stroop test, parts D and C; Digit Span and Visual Memory Span (VMS) from the WMS-R; the California Verbal Learning Test (CVLT); word recall and stem completion task; CFQ; and parts of the Coping Strategies Questionnaire.

Except for a weak association with the Stroop test ($r = 0.28$, $p < 0.05$), self-reported measures of cognitive dysfunction via the CFQ did not correlate with any of the scores obtained on neuropsychological tests. Depression scores correlated with

[162] Townsend LA. Chronic pain and cognition: effects of pain intensity on tasks of attention and memory. Digital Dissertation. University of Victoria (Canada). 1996; 124p.
[163] Ibid.

CFQ scores ($r = 0.59$, $p < 0.001$), and no association was found between pain intensity and CFQ. The Stroop C test and the semantic cluster ratio of the CVLT (measures of effortful processing) and Stroop D test (automatic processing) accounted for only 2 percent of the variance in pain intensity. Pain intensity did not affect either explicit (measured by Free recall and CVLT trials A1-A5) or implicit memory in this sample, as these tests accounted for 2 percent and 3 percent of the variance respectively. The Digit span and the PASAT (verbal function measures) and VMS (nonverbal processing) accounted for 3 percent of the variance in pain intensity. Thus, pain intensity did not impact cognitive function and only the Digit Span and the CVLT were significantly correlated with this measure. This study was associated with several limitations. Many patients rescheduled appointments due to severe pain. At the time of testing, pain may have not been substantial to affect cognitive processes. Since cognitive deficits may be mild to begin with, tests involving complex tasks may have been more suitable in this population. The reviewed evidence indicates that pain intensity does not correlate with cognitive function; thus, the premise utilized in this study may be inappropriate. In a more recent study, Pincus and Newman found that recall bias was significantly ($p = 0.02$) associated with utilization costs (referrals to specialists) for back pain.[164]

Sletvold and colleagues assessed neuropsychological functioning in a sample of fibromyalgia patients ($n = 25$), depressed patients ($n = 22$), and healthy controls.[165] Only FM patients reported pain intensities on a VAS. A 3-way multivariate analysis of covariance showed significant differences ($p < 0.05$) in cognitive ability scores for the three groups. While the two patient groups did not differ significantly, FM group had significantly lower scores on the Digit symbol test [$F(1,40) = 5.6$, $p< 0.05$], PASAT (presentation rate 2.4 seconds) [$F(1,40) = 4.1$, $p< 0.05$], PASAT (presentation rate 2.0 seconds) [$F(1,40) = 4.1$, $p< 0.05$], reaction time with left hand [$F(1,40) = 4.1$, $p< 0.05$], and reaction time with left hand utilizing an inhibiting

[164] Pincus T, Newman S. Recall bias, pain, depression and cost in back pain patients. *British Journal of Clinical Psychology*. 2001;40:143-156.
[165] Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression, and healthy controls. *The Journal of Rheumatology*. 1995;22:137-142.

stimulus than the controls. Depressed patients scored significantly worse than controls on these tests as well. A subsequent analysis showed that FM (n = 11) patients with and without lifetime history of depression (n = 14) did not differ significantly on the cognitive test scores. These results indicated that pain patients do experience cognitive dysfunction, and factors in addition to affect disorder are associated with this dysfunction. Although medication use of depressed patients was assessed (no antidepressants, lithium carbonate, or neuroleptics agents used in previous month), this assessment was not performed for FM patients.

Landro and colleagues also reported results from the same groups of subjects on the Randt Memory Test, The Code Memory Test, The Word Fluency Task, The Kimura Recurring Recognition Figures Test, and the Incidental Memory Task, all tests of long term memory.[166] The tests indicated that FM patients with a lifetime depressive disorder and depressed patients scored significantly lower on the on the Randt Memory Test [$F(1,40)= 6.1$, $p < 0.05$]; [$F(1,37) = 13.5$, $p < 0.001$, respectively], Word Fluency Task [$F(1,40) = 5.5$, $p < 0.05$; [$F(1,37) = 0.9$, $p < 0.001$, respectively], and Code Memory Tests part 1 [$F(1,40) = 7.6$, $p < 0.01$; [$F(1,37) = 11.3$, $p < 0.01$, respectively], and Code Memory Tests part 2 [$F(1,40) = 8.6$, $p < 0.01$; [$F(1,37) = 5.3$, $p < 0.05$, respectively].

Iezzi and colleagues tested a sample of chronic nonmalignant pain patients (n = 73) on several neuropsychological tests including the Wechsler adult intelligence scale, the Wechsler memory scale – Revised, the Rey-Osterrieth figure test, the Stroop test, the Wisconsin card sorting test, the PASAT, the trail making test, form B, the design fluency test, the COWA, and the grooved pegboard test.[167] A cluster analysis was used to classify patients as having high, moderate, or low levels of distress based on responses to the SCL-90-R. Patients with low distress on average had more education (years) (low, n = 10, mean = 13.5, s.d. = 3.4), (high, n = 27 mean = 11.6, s.d. = 2.5); (moderate, n = 36, mean = 12.7, s.d. = 2.3); and less pain duration

[166] Landro NI, Stiles TC, Sletvold H. Memory functioning in patients with primary fibromyalgia and major depression and healthy controls. *Journal of Psychosomatic Research*. 1997;42;297-306.
[167] Iezzi T, Archibald Y, Barnett P, Klinck A, Duckworth M. Neurocognitive performance and emotional status in chronic pain patients. *Journal of Behavioral Medicine*. 1999;22:205-216.

(low, mean = 65.7, s.d. = 70.7), (high, mean = 118.8 months, s.d. = 146.4); (moderate, mean = 59.1, s.d. = 42.2). A multivariate analysis of variance showed significant differences between the groups on cognitive function tests. Post hoc Scheffe's test showed that the low and moderate distress groups performed significantly better than the high distress group on the Rey-Osterreith figure test ($p < 0.05$), Stroop test ($p < 0.05$), PASAT ($p < 0.05$), and visual memory component of the Weschler memory scale ($p < 0.005$). The low distress group also outperformed ($p < 0.05$) the high distress group on the Weschler adult intelligence scale. The differences in education level and pain duration were not considered in the analyses; additionally high distress patients were believed to be on narcotic and psychotropic medications, and prior research has demonstrated that psychotropics impair performance on cognitive tests.

A recent study included a broad array of predictors such as demographics, pain severity and location, psychological distress, anxiety, quality of sleep, prescription drug use, and involvement in lawsuits on cognitive functioning.[168] The Alertness Behavior subscale of the Sickness Impact profile was used to assess cognitive difficulties associated with completion of daily tasks. Of 275 patients enrolled in the study, 64 (23.4%), 63 (23.1%), 51 (18.7%), and 56 (20.5%) chronic pain patients reported problems with forgetfulness, minor accidents, and difficulty with maintaining attention and completion of tasks, respectively. Depression scores obtained through the BDI and use of antidepressant medications were significantly ($p < 0.01$) correlated with cognitive complaints, while the association with pain-related anxiety approached significance ($p = 0.08$). These variables contributed 36 percent of the variance to patient reports of difficulties with daily tasks. Use of narcotic analgesics did not seem to negatively affect cognitive abilities. McCracken and Iverson state that the relationship "between cognitive impairment, opioid use, and depression in patients with chronic pain deserve further study."[169]

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[168] McCracken LM, Iverson GL. Predicting complaints of impaired cognitive functioning in patients with chronic pain. *Journal of Pain and Symptom Management*. 2001;5:392-396.
[169] Ibid

Grace and colleagues compared 30 fibromyalgia patients to an equal number of healthy controls on a series of neuropsychological tests including the Wechsler Memory Scale – Revised (WMS – R), Rey-Auditory Verbal Learning Test, PASAT, Symbol Digit Modalities Test (SDMT), Memory Observation Questionnaire, and pain severity scale of the Multidimensional Pain Questionnaire.[170] A multivariate analysis of variance indicated that FM patients performed significantly ($p < 0.0001$) poorly compared to controls. Healthy controls performed significantly ($p < 0.05$) better on the WMS – R and PASAT, while differences on the SDMT approached significance. Patients had greater trouble with tasks that required sustained attention. Even though self-reports of attention deficits were greater for patients than controls, this difference was not reflected on objective testing. Anxiety levels, and not pain severity was correlated significantly wth delayed recall, memory, and PASAT.

In contrast, some researchers have also hypothesized that cognitive functioning, in addition to pain and self-efficacy, contribute to mental health of pain patients. Shifren and colleagues have measures intellectual (cognitive) functioning by gauging performance on tasks involving "working memory", "speed of processing information," "verbal ability," and "reasoning."[171] It has been suggested that patients with higher levels of intellectual functioning can devise more suitable strategies to treat their condition better, and do not tend to focus on negative outcomes as much as individuals with limited cognitive abilities.

The following measures were used to assess intellectual functioning: free recall, reading and computation span tasks as indicators of working memory, letter and pattern comparison tasks as measures of perceptual speed, identification of synonyms to assess verbal ability, and letter set test as an indicator of reasoning.[172] Mental health was assessed using the Center for Epidemiologic Studies Depression Scale (CES-D) and the Multiple Affect Adjective Checklist – Revised (MAACL-R-R), the

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[170] Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology*. 1999;21:477-487.
[171] Shifren K, Park DC, Bennett JM, Morrell RW. Do cognitive processes predict mental health in individuals with theumatoid arthritis. *Journal of Behavioral Medicine*. 1999;22:529-547.
[172] Ibid

latter is capable of delineating positive affect from negative affect. The structural equation model included pain, self-efficacy, and intellectual functioning, which explained 45 percent and 62 percent of variance in positive and negative affect, respectively. Age and education influenced the dependent variable indirectly, through intellectual functioning. Pain was related only with negative affect.

A review of the literature indicates that chronic nonmalignant pain patients experience mild cognitive deficits. Deficits may be observed in the following areas: sustained attention, memory, arithmetic, and other tasks requiring concentration. Often, this association is mediated by numerous variables such as high intensity pain, depression, anxiety, and minimal participation in activities or lack of a desire to participate in various social activities. Patient performance on the Digit Symbol test, PASAT, reaction time tests, Stroop tests, and some tests of memory seemed to have been impaired. Many of the studies addressing cognitive appraisals in chronic pain patients have failed to examine the issue within a theoretical context. The review above has demonstrated that numerous factors influence cognitive deficits among pain patients. Pain also has been widely recognized as a multidimensional experience. Thus, the study of cognitive function in patients with chronic nonmalignant pain deserves a systematic approach that is based on certain theoretical principles.

1.3.13 Effects of Experimentally Induced Pain on Attention

The review above clearly indicates that pain has the ability to capture attention and draw attention away from a variety of tasks. There is substantial documented evidence to indicate that attention-based cognitive coping strategies help chronic pain patients obtain analgesic relief through the modification of pain perception.[173] However, these effects have been demonstrated primarily in controlled laboratory settings. Even though numerous studies have addressed the effects of various

[173] Eccleston C. The attentional control of pain: methodological and theoretical concerns. *Pain.* 1995;63:3-10.

distraction tasks, limited research has focused on the interruptive ability of experimentally induced pain on tasks. In addition to stimuli that are threatening or noxious, it can be hypothesized that novel stimuli such as experimentally induced pain would also be capable of interfering with attention.

Crombez and colleagues tested two competing models regarding the effect of knowledge about impeding pain.[174] According to one model, prior knowledge sensitizes individuals leading them to process information at an emotional rather than analytical level. As a result, even the hint of a painful stimulus can be perceived as noxious if the message was thus perceived. On the other hand, "cognitively oriented representation models" suggest that individuals are capable of structuring expectations so as to simulate an event very closely. Such an accurate anticipation typically minimizes the actual impact of the event. "Thus, when the objective stimulus is unambiguously painful, a pain warning may enhance the accuracy of the representation, which would result in a better match and consequently in a lesser impact.[175]"

Crombez and colleagues studied the effects of painful stimuli (46° C) on the ability to discriminate between a low-pitched and high-pitched tone.[176] In order to test the emotion-based and cognitive-based models, distractors such as slides with a picture and warmth stimuli were introduced. A 2 X 2 design was employed; half of the participants (n = 42) were informed (temporal certain group) about the timing of distractor presentation while the other half were not. Also one half (pain condition) of the participants were told that that warmth stimulus was intense and perceived as painful to most individuals. Individuals expecting the painful stimulus provided lower intensity ratings for the heat stimuli (mean = 20.67) than the other group (mean = 27.59). It was reasoned that subjects in the pain group overestimated the pain intensity of the impending stimulus. An opposite effect could have resulted if pain

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[174] Crombez G, Baeyens F, Eelen P. Sensory and temporal information about impending pain: the influence of predictability on pain. *Behavior Research and Therapy*. 1994;32:611-622.

175 Ibid.

176 Ibid.

intensities were underestimated, subjects may have perceived the stimuli to be intense. Reaction time to the auditory task were slowed only by the heat distractor and not the slide distractor lending further support to the hypothesis that pain interferes with attention.

An experiment was used to determine the effects of painful/control stimuli on the ability to distinguish between a high pitched and low pitched tone.[177] Subjects reported the pain stimuli to be intense and unpleasant (mean = -1.8) as compared to control stimulus (mean = 0.24, +5 = pleasant, -5 = unpleasant) {t (25), $p < 0.001$}, and subjects reported being significantly {t (25), $p < 0.001$} more distracted with pain stimuli (mean = 6.45) than with control stimulus (mean = 4.49). Standard deviation scores were not reported. Distraction was rated on an 11-point scale with 0 being "not at all distracted" and 10 being "very strongly distracted." Results from the study showed that painful stimuli produced significantly greater disruption in task completion than control stimuli. Even though control stimuli increased reaction time for the completion of the auditory discrimination task, the effects were not as dramatic as those observed with the pain stimuli. Stimuli were administered at three intervals and the extent of disruption continued to decline with subsequent stimuli so that no differences in reaction time were observed due to administration of either pain or control stimuli at interval three.

The authors draw on several theories to address the implications of the above results. New stimuli trigger alarm systems that draw a significant amount of attention thereby increasing the amount of time required or the number of errors in the process of task completion. Responses to these stimuli after they have lost their novelty are governed by motivational-affective systems, which utilize different mechanisms. In this scenario, pain stimuli did not pose any imminent or long-term threat value; therefore, participants in the experiment were able to compensate for any attentional deficits and complete the task without much difficulty on subsequent attempts. It has

[177] Crombez G, Eccleston C, Baeyens F, Eelen P. The disruptive nature of pain: An experimental investigation. *Behaviour Research and Therapy*. 1996;34:911-918.

also been recognized that processes involving attention compensate continuously to maintain coherence and are capable of minimizing the effects of any extraneous stimuli. "It is remarkably difficult to demonstrate serious degradations in performance during the presence of stressors."[178] We saw here that participants were able to voluntarily focus attention on the task after adjusting to the pain stimulus. Pain intensity did cause interruption and subsequent reduction in response was due to the ability to compensate. In the context of chronic pain where pain intensity may flare on occasions, and the distress and suffering arising from these stimuli and perceptions about harm associated with pain could affect the ability to refocus attention in these patients. This pattern of interference can lead to deficiencies in several cognitive domains among chronic pain patients.[179]

Crombez and colleagues, in an effort to understand the effect of varying pain intensities on task interference and the process of recovery with respect to task interference administered electric stimuli to a sample of healthy volunteers (n = 24). It was observed that pain and control stimuli disrupted attention at first, measured by excess time and/or greater inaccuracy in the completion of an auditory task compared to baseline. Results showed that on subsequent administration of stimuli, pain continued to disrupt attention while control stimulus did not distract from the task. Greater effort was required to divert attention away from the pain stimulus.[180] The pain stimulus continued to disrupt attention even at subsequent administrations, contrary to the findings presented above. The authors suspected that methodological differences in the current study and that presented above (Crombez G et al., 1996) are responsible for this discrepancy. Even though the effect of pain on task interference persisted, a gradual reduction in response times indicates that subjects can adapt to experimental pain stimuli.

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[178] Ibid

[179] Crombez G, Eccleston C, Baeyens F, Eelen P. The disruptive nature of pain: An experimental investigation. *Behaviour Research and Therapy*. 1996;34:911-918.

[180] Crombez G, Eccleston C, Baeyens F, Eelen P. Habituation and the interference of pain with task performance. *Pain.* 1997;70:149-154.

In another study, Crombez and colleagues subjected participants (n=37) to an elecrocutaneous stimulus and a control stimulus.[181] The purpose of the study was to distinguish the extent to which threat of pain moderated subjects' responses to an auditory discriminating task [high (1000 Hz) and low tones (250 Hz)]. A control group (n =19) was informed about the maximum intensity of stimulus that would be generated, while the threat group (n =18) was notified about the possibility of stimuli with fluctuating intensities. The results indicated that electrocutaneous stimuli rather than control stimuli produced significantly higher reaction times in the high threat group than in the control group. It has been postulated that fear of harmful consequences evoked by threats are capable of inducing avoidance behaviors. For chronic pain patients that have developed a sense of fear of their condition, participation in activities/behaviors that can trigger pain are avoided and considerable attentions is devoted to a variety of triggers.

The effect of catstrophizing about pain on attention has also been examined. Prior research has suggested that patients who magnify the potential effects of pain and the threat pain poses are preoccupied with its effects and find it difficult to refocus attention on other tasks. A similar task-oriented procedure as has been described above was utilized.[182] A painful stimulus was delivered via electrodes to both arms, and participants were threatened by informing them about the delivery on an intense stimulus to one arm (right/left), while the other arm received a constant level of low-intensity stimulation. Data on catastrophizing (Pain Catastrophizing Scale -PCS), negative, and positive emotions were also collected. A median split based on PCS scores were used to identify catastrophizers (n = 20, mean = 23.05, s.d. = 5.47) fron non-catastrophizers (n = 23, mean = 9.52, s.d. = 4.47). Catastrophizers were found to have greater levels of negative affect and lower levels of positive affect. Ratings about intensity of threat stimulus provided by the two groups were similar. Results indicated that task interference was pronounced for catastrophizers in

[181] Crombez G, Eccleston C, Baeyens F, Eelen P. Attentional disruption is enhanced by the threat of pain. *Behavior Research and Therapy*. 1998;36:195-204.
[182] Crombez G, Eccleston C, Baeyens F, Eelen P. When somatic information threatens, catastrophic thinking enhances attentional interference. *Pain*. 1998;75:187-198.

the presence of threat stimuli, however this effect was observed only at Time 1 and not during subsequent test administration. Task interruption due to the low-intensity stimulus was pronounced in these individuals, who also rated the stimulus as being more intense and unpleasant. These results indicate that catastrophizing does mediate the interruptive effect of pain.

In comparison to the laboratory setting, a real fear of pain may have more lasting effects than those observed in the present study. A cross-sectional study about coping styles in chronic pain showed that avoidance behaviors were highly prevalent.[183] Avoiders did not differ from pain confronters in either pathology or self-reports about pain intensity. Avoidance behaviors are commonly observed in catastrophizers indicating an association between these behaviors and attention deficits. A recent study conducted with healthy individuals indicates that the association between pain and fear may be spurious.[184] The experimental procedure use to induce pain (inflating a sphygmomanometer cuff around the forearm) may have contributed to the results, as the stimuli may have not been perceived as harmful.

In summary, novel stimuli such as experimentally induced pain can interrupt attention. Typically, individuals can adapt to successive stimuli and are capable of refocusing their attention. It can be reasoned that pain stimuli in a laboratory setting do not have any lasting threat value, and are therefore incapable of capturing attention subsequently. Factors such as the threat of pain, catastrophizing, and negative affect are associated with the interruption function of pain.

[183] Crombez G, Vervaet L, Lysens R, Baeyens F, Eeleen P. Avoidance and confrontation of painful, back straining movements in chronic pain. *Behavior Modification*. 1998;22:62-77.
[184] Roelofs J, Peters ML, Vlaeyen JWS. Selective attention for pain-related information in healthy individuals: the role of pain and fear. *European Journal of Pain*. 2002;6:331-339.

1.3.14 Effects of Opioids on Cognition in Healthy Subjects

There is extensive literature that documents the effectiveness of morphine and other opioids on cognitive status in health subjects. A study that examined the effects of morphine in experimentally induced pain induced conducted as early as 1940 concluded that feelings of calmness and satisfaction that may occur under normal conditions of morphine administration do not persist in the presence of painful stimuli.[185] Numerous studies have examined the effects of opioids in healthy subjects.

Zacny has provided a comprerehensive review about the effects of opioids on psychomotor and cognitive functioning in humans.[186] The review was structured to provide information about the type of opioids considered, studies examining psychomotor and cognitive effects of opioids, effects of opioid withdrawal in physically dependent subjects, and epidemiological aspects including the correlation between opioid use and accidents. Studies reviewed examined the effects of morphine agonists (morphine, hydromorphone, heroin, merperidine, fentanyl, alfentanyl, and methadone), partial agonists (oxycodone and dihydrocodeine, propoxyphene, dextropropoxyphene, dipipanone, meptazinol, papaveratum, and dezocine), and mixed agonist-antagonists (buprenorphine, pentazocine, butorphanol, and nalbuphine).

Effects on Motor Tasks and Reaction Times:

Among three studies with healthy subjects, morphine impaired reaction time (RT) measured as finger tapping in only one experiment. Among chronic cancer pain patients, dose escalation was associated with increased reaction time measured by tapping rate. However, psychomotor effects subsided within a week. Morphine doses of 10mg, 15mg, and 30 mg have been found to increase auditory reaction times. Two studies examined the extent to which external stimuli (shock) modified cognitive

[185] Wolff et al. Cited by: Conley K, Toledano AY, Apfelbaum JL, Zacny JP. Modulating effects of a cold water stimulus on opioid effects in volunteers. *Psychopharmacology*. 1997;131:313-320.
[186] Zacny JP. A review of the effects of opioids on psychomotor and cognitive functioning in humans. *Experimental and Clinical Psychopharmacology.* 1995;3:432-466.

effects as measured by visual RT test. Although morphine did produce a higher RT time than saline, there was no difference in RT time between groups administered morphine, shock, or a combination. Surprisingly, combination of shock and morphine resulted in fewer disruptive effects than the administration of morphine alone. The suggestion that morphine does not worsen, and may even improve pain-induced impairment can be traced as far back as 1952.

Of three studies that assessed the effects of IV fentanyl (20mg morphine equivalent dose), only results from one experiment showed an impaired performance on finger tapping. Visuo-motor tracking in healthy subjects on fentanyl was impaired in one study (morphine equivalent dose – 10 mg) and unaffected in another (morphine equivalent dose – 5 mg) demonstrating a dose-response relationship. Oxycodone (morphine equivalent dose – 9.1 mg) did not compromise finger tapping speed.[187]

Effects on Information Processing

The Digit Symbol Substitution Test (DSST) was used to examine the effects of morphine (dose range – 0 to 10mg) in four different studies among healthy volunteers. Volunteers showed no impairment except in one study, and effects of the drug were not very strong when compared to placebo (only four fewer symbols were incorrectly substituted). In studies that evaluated the effects of morphine/hydromorphone (dose range – 0 to 30mg) on the DSST among opioid abusers, results were no different than those obtained with placebo. The tests were performed with a maximum dose equivalent to 30mg of morphine. In similar tests that were conducted among opioid dependent individuals, doses of either morphine or hydromorphone that ranged from 0.125 mg to 14mg equivalents of morphine produced no significant differences in performance compared to placebo. Among studies (n = 7) that have examined the effects of 10mg morphine on the speed and accuracy of oral addition, written addition, arithmetic, and coding and all but one

[187] Ibid.

have detected impairment in speed. Only one study concluded that accuracy on a written addition test was compromised.[188]

Fentanyl administered via infusion impaired performance on the DSST among healthy volunteers, the relationship was dose-dependent. A low dose of fentanyl (morphine equivalent dose – 5mg) administered as an injection and intramuscularly administered oxycodone (morphine equivalent dose – 9.1 mg) did not impair ability to perform on the DSST compared to placebo.

Effects on Sustained Attention:

Sustained attention has been measured using RT tests that last for 5 to 10 minutes. In a comparison of intravenous infusion, oral, and sustained release dosage forms in healthy volunteers, only IV morphine impaired a sustained auditory task. Comparison between cancer patients (morphine dose range – 10 - 307 mg) and healthy controls (no drug) yielded impaired performance on a 10 minute auditory reaction time test. Performance on tasks such as hidden figures test (complex pictures containing simpler ones to be identified) and penning numbers in the order presented have suffered after administration of morphine in healthy volunteers.[189]

Considerably large doses of IV fentanly (morphine equivalent dose – 20 mg) and relatively small dose of oxycodone (morphine equivalent dose – 3 mg) administered subcutaneously (SC) did not affect performance on the symbol cancellation test.

Effects on Complex Psychomotor Performance:

Morphine doses (as high as10mg) in healthy subjects have not impaired cognitive tasks such as complex tracking and ability to solve orally presented arithmetic problems in the presence of distraction. The effects of (SC) oxycodone (morphine equivalent dose – 9.1 mg) on three complex cognitive tests were

[188] Ibid.
[189] Ibid.

evaluated: divided attention, tracking, and choice reaction time (CRT). A negative effect on performance was observed only in the case of CRT.[190]

Effects in Memory (Immediate Recall)

One study (Digit Span Test) in healthy volunteers and four in opioid dependent individuals (Immediate Free Recall) found no impairment on tests due to morphine. In two studies conducted by the same author that utilized immediate free recall testing, IV fentanyl (morphine equivalent dose – 21mg) did not impair performance. A third study that assessed performance on free recall, Digit span, and the Benton visual retention tests found that IV fentanyl (morphine equivalent dose – 21mg) impaired performance only on the Digit Span. Test. Another study found the opposite result (improved performance on Digit Span) in the case of SC oxycodone (morphine equivalent dose – 3 mg).[191]

Effects on Memory (Delayed Recall):

Studies assessing delayed recall have found that morphine does not negatively affect recall, however, reading speed has been shown to be compromised. Neither fentanyl nor oxycodone in any of the studies reviewed were found to negatively affect delayed free recall. Fentanyl has been shown to decrease reading speed.

Jarvik and colleagues examined the effects of morphine (10mg/70 kg body weight) on pain tolerance and psychomotor function measured by the Digit Symbol Substitution (DSS) test and the finger tapping test.[192] Tests were administered at three time intervals: 45 minutes before and 45, 225 minutes after the dose. The study included 20 subjects (10 monozygotic twin pairs) who were subjected to experimental pain using the cold pressor technique. Morphine significantly ($p < 0.05$) increased pain tolerance. Performance on the DSS improved significantly ($p < 0.05$) after administration of morphine as compared to placebo. Performance on the FTT declined significantly ($p < 0.05$) after session two with administration of both placebo and morphine. In the case of DSS test, the authors cited practice effects as the reason

[190] Ibid
[191] Ibid.
[192] Jarvik LF, simpson JH, Guthrie D, Liston EH. Morphine, experimental pain, and psychological reactions. *Psychopharmacology*. 1981;75:124-131.

for improved performance, while in the case of FTT, fatigue was associated with the decline in performance.

A group of eight healthy volunteers were selected to examine the effects of placebo, 20mg dihydrocodeine, and D-Met^2 Pro^5-enkephalinamide (EA –3 and 10mg) each administered 2-3 weeks apart on pain tolerance and cognitive function.[193] Pain was experimentally induced using a sub maximum effort tourniquet technique. The following cognitive tests were administered: symbol cancellation test, digits forward and backward test, and the Guilford memory test. Dihydrocodeine and EA 10mg enhanced pain threshold at 30 and 60-minute intervals. As compared to placebo, performance on the symbol cancellation and digits forward and backwards test improved subsequent to administration of drugs. Treatment did not produce an effect on the word fluency test.

Stacher and colleagues utilized electrical and thermal stimulation techniques to induce pain in a sample of 48 subjects to assess the analgesic effects of orally administered diclofenac sodium (75 and 150 mg), codeine (60mg), and placebo.[194] Psychomotor function was measured as a function of sensorimotor responsiveness and fine motor control. Reaction time to acoustic stimuli was used to measure the former and subjects were required to complete a tracking task in order to assess motor control. Diclofenac 150 mg, codeine 60mg, and diclofenac 75mg in this order significantly ($p < 0.05$) increased pain threshold and tolerance as compared to placebo. As compared to placebo and diclofenac 150mg, reaction time to acoustic stimuli was significantly ($p < 0.05$) higher for diclofenac 75 mg and codeine 60mg. The effects of codeine on fine motor control were similar to that of placebo.

[193] Szekely JI, Torok K, Karczag I, Tolna J, Till M. Effects of D-Met^2 , Pro^5-enkephalinamide on pain tolerance and some cognitive function in man. *Psychopharmacology*. 1986;89:409-413.
[194] Stacher G, Steinringer H, Schneider S, Mittelbach G, Winklehner S, Gaupmann G. Experimental pain induced by electrical and thermal stimulation of the skin in healthy man: sensitivity to 75 and 150 mg diclofenac sodium in comparison with 60 mg codeine and placebo. *British Journal of Clinical Pharmacology*. 1985;21:35-43.

Bradley and Nicholson assessed the cognitive effects of codeine (30, 60, and 90mg) and triprolidine (10mg) on six healthy subjects.[195] Cognitive functioning was assessed as performance on the following tests: visuo-motor coordination (VMC), dynamic visual acuity (DVA), complex reaction time (CRT), critical flicker fusion (CFF), and digit symbol substitution test (DSST). Codeine (60 and 90mg doses) impaired performance on the VMC as measured by difference in mean scores obtained from the two test intervals (time 1 and time 2) as compared to mean score difference when placebo was administered. Codeine 90mg and troprolidine impaired performance on the DVA. Codeine did not affect performance on the CRT, CFF, and DSST. Poor visuo-motor coordination was associated with nausea and not drowsiness or sedation.

A randomized double blind cross over single dose trial was used to assess the effects of morphine sulphate (10mg and 15mg), lorazepam (1mg), and placebo in twelve healthy subjects over a period of four weeks.[196] Drug effects (baseline, 1, 2, 4, and 6 h after administration) were observed on the following cognitive function tests: simple reaction time, choice reaction time, number vigilance, (all 3 tests of attention) memory scanning, immediate and delayed word recall, word recognition, picture recognition (tests of memory), critical flicker fusion threshold (CFFT). Compared to placebo, morphine sulphate (10mg and 15mg) significantly ($p < 0.05$) impaired performance on the delayed word recall and picture recognition test at the one-hour interval, and performance at subsequent intervals was not compromised. Performance on the CFFT declined steadily, and was significantly lower for both doses compared to placebo at the 4-hour interval. Lorazepam impaired performance on all tests.

O'Neill and colleagues utilized a similar study design as described above to ascertain the cognitive effects of dextropropoxyphene napsylate 100mg, morphine

[195] Bradley CM, Nicholson AM. Effects of a μ-opioid receptor agonist (codeine phosphate) on visuo-motor coordination and dynamic visual acuity in man. *British Journal of Clinical Pharmacology*. 1986;22:507-512.

[196] Hanks GW, O'Neill WM, Simpson P, Wesnes K. The cognitive and psychomotor effects of opioid analgesics. *European Journal of Clinical Pharmacology*. 1995;48:455-460.

sulphate 10mg, lorazepam 0.5mg, and placebo in ten healthy subjects.[197] Lorazepam significantly ($p < 0.05$) impaired reaction time on all tasks at time intervals ranging from four hours to 30 hours (list of tasks provided in Hanks GW et al. summary) except the digit vigilance task. Dextropropoxyphene negatively affected performance on choice reaction time and picture recognition tests at several time intervals. The effects of morphine in comparison were negligible. Although accuracy on the choice reaction time improved significantly ($p < 0.005$), speed declined. The improvement in accuracy had been observed in their previous study (Hanks GW et al., 1995) as well. Additionally morphine impaired speed on the simple reaction time (16 h, $p = 0.05$, 36 h $p < 0.01$), negatively affected memory scanning sensitivity and speed (12h, $p < 0.005$; 16h, $p < 0.02$). In light of the inconsistent results observed with morphine (stong mu agonist) in comparison with dextropropoxyphene (weak mu agonist), the authors concluded that larger doses of morphine may produce a more pronounced cognitive effect. However, the results clearly indicate that in comparison to lorazepam, the effects of both strong and weak mu agonists on cognitive function are minor. Larger doses of morphine taken chronically may be associated with a general slowing of reaction time; however, this effect in the context of a pain patient, the dosage form, and route of administration can be variable.

Conley and colleagues examined the effects of equianalgesic doses of morphine and Butarphanol administered intravaneously on psychomotor function.[198] A total of 13 subjects were examined in the presence of a painful stimulus (cold pressor) and a control condition. While butarphanol impaired performance in both conditions, morphine did not impair performance on the Digit Symbol Substitution Test. This may be explained by the different receptors that morphine (mu) and butarphanol (kappa) affect.

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[197] O'Neill WM, Hanks GW, Simpson P, et al. The cognitive and psychomotor effects of morphine in healthy subjects: a randomized controlled trial of repeated (four) oral doses of dextropropoxyphene, morphine, lorazepam and placebo. *Pain.* 2000;85:209-215.

[198] Conley K, Toledano AY, Apfelbaum JL, Zacny JP. Modulating effects of a cold water stimulus on opioid effects in volunteers. *Psychopharmacology*. 1997;131:313-320.

Walker and Zacny found that oral morphine (40mg) did not impair performance on any psychomotor tests such as DSST, auditory reaction test, logical reasoning test, and locally developed short term and long term memory tests.[199] However, this dose did cause sedative effects as measured by the penotobarbital-chlorpromazine-alcohol (PCAG) subscale of the addiction research center inventory (ARCI) used to distinguish various classes of psychoactive drugs. Hill and Zacny examined the psychomotor effects of hydromorphone (0, 0.33, 0.65, 1.3mg/70kg) and morphine (5 and 10mg/70kg) in a group of 17 health non-drug abusing subjects.[200] A significantly ($p < 0.05$) lower score was obtained on the DSST for subjects on the largest dose of hydromorphone (Hydromorphone Dose –1.3mg/70kg, Mean DSST score = 42.3, sd =2.7) than when subjects were on saline (Mean DSST score = 46.3, sd = 2.2). According to the authors, the decline in performance is minimal in comparison to those observed with benzodiazepenes and other sedatives (15-20 fewer symbols). Subjects on morphine (10mg/70kg) performed comparably on the DSST (Mean score = 43.6, sd = 2.4), however, a 1.3mg/70kg dose of hydromorphone is equivalent to 13.4mg of morphine. Both drugs did not affect reaction time, hand-eye coordination, logical reasoning or memory processes.

In a recent study, Walker and colleagues examined the effects of administering increased doses of either morphine or nalbuphine (0, 2.5, 5, and 10mg/70kg), butorphanol (0, 0.5, 1, and 2 mg/70kg), pentazocine (0, 7.5, 15, and 0mg/70kg), or saline.[201] Results showed that increasing doses of opioids (except for pentazocine) caused impaired performance on the DSST. While the rate at which symbols were drawn were affected, accuracy was not compromised. Cognitive impairment as assessed by decreasing number of symbols was observed after the fourth dose for morphine (6 fewer symbols) and nalbuphine (10 fewer symbols), and after third dose

[199] Walker DJ, Zacny JP. Subjective, psychomotor, and analgesic effects of oral codeine and morphine in health volunteers. *Psychopharmacology.* 1998;140:191-201.
[200] Hill JL, Zacny JP. Comparing the subjective, psychomotor, and physiological effects intravenous hydromorphone and morphine in healthy volunteers. *Psychopharmacology*. 2000;152:31-39.
[201] Walker DJ, Zacny JP, Galva KE, Lichtor JL. Subjective, psychomotor, and physiological effects of cumulative doses of mixed-action opioids in healthy volunteers. *Psychopharmacology*. 2001;155:362-371.

of butorphanol (23 fewer symbols). Butorphanol also affected hand-eye coordination to a greater extent than morphine and nalbuphine. Only butorphanol impaired perfomance on the logical reasoning test.

Most recently, Allen and colleagues compared the effects of placebo, ibuprofen, and a combination of hydrocodone bitartrate (7.5mg) and ibuprofen (200 mg) on sustained attention, concentration, and coordinated movement.[202] Participants included 72 healthy males who were subjected to exercise induced muscle damage. The following cognitive tests were utilized: PASAT; tracking task (2 measures, i.e., percentage of time on track and total possible distance successfully tracked); and simple as well as complex reaction time. It was observed that participants on combination therapy (mean = 58.06, SEM = +/- 0.85) obtained significantly ($p < 0.03$) lower score for the percent of time on track compared to ibuprofen (mean = 61.35, SEM = +/- 0.85), but not placebo (mean = 59.21, SEM = +/- 0.85). Even though this group committed a significantly greater number of errors on simple reaction time task then the two other groups, they performed the task much faster as well, which may have contributed to the inaccuracy. In conclusion, hydrocodone did not produce any systematic cognitive effects among participants.

Many of the studies examined here were one-time dose experiments or tested multiple doses over several weeks. Based on the findings reported in these studies, it can be concluded that opioids (morphine, fentanyl, oxycodone, codeine, and hydromorphone) do not significantly impair cognitive status in healthy subjects. Impairments were observed most commonly in tests of motor function. Tasks assessing attention, information processing, and memory were not hampered by these drugs except with very large doses.

[202] Allen GJ, Hartl TL, Duffany S, Smith SF et al. Cognitive and motor function after administration of hydrocodone bitartrate plus ibuprofen, ibuprofen alone, or placebo in healthy subjects with exercise-induced muscle damage: a randomized, repeated-dose, placebo-controlled study. *Psychopharmacology.* 2003;166:228-233.

1.3.15 Effects of Opioids on Cognitive Ability in Chronic Non -Malignant Pain (CNMP) Patients

The target population for the proposed study is chronic nonmalignant pain patients who will be treated with long-acting narcotic analgesics. Thus, it is necessary to review the literature examining the effects of opioid use on cognitive status among CNMP patients.

McNairy and colleagues observed patients on narcotic analgesics that faced difficulty in focusing, understanding, and retaining instructions provided upon entry at a clinic.[203] Observations were made over a three day period and patients controlled medication consumption frequency. The following cognitive function tests were administered: Wechsler verbal performance, full scale IQs, digit symbol, and block design, which are subscales of the Wechsler test; tactual performance test (TPT), finger tapping test, grooved pegboard test, and Rey's auditory-verbal learning test (AVLT). Patients were designated as non-abusers (mean daily dose = 2.36 mg), abusers (mean daily dose = 18.6 mg), or dependent users (mean daily dose = 32.3 mg) based on narcotic analgesic consumption expressed as milligram equivalents of morphine. On average, abusers (mean daily dose = 188 mg) and dependent users (mean daily dose = 520 mg) consumed significantly greater amounts of tranquilizers (expresses as milligram units of pentobarbital) than non abusers (mean daily dose = 15mg). The abuse-dependent groups were combined into one group for analyses, and demonstrated impaired performance on the digit symbol ($p = 0.005$), block design ($p = 0.008$), TPT – dominant, nondominant, both hands ($p = 0.006$, $p = 0.01$, $p = 0.014$). The verbal test suggested that both groups did not display any aberrant memory or learning functioning.

Although the results of this study suggest that use of high dose narcotics is associated with cognitive impairment, several limitations are associated with the study methodology and analyses of data. Numerous (54) ANOVAs were conducted thereby inflating alpha error. The authors did not utilize any corrective measures,

[203] McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. *Pain*. 1984;18:169-177.

such as Bonferroni's test to adjust for this inflation. Abusers and dependent users utilized excess doses of narcotics and as such these patients cannot be compared to chronic pain patients without deviant drug taking behaviors. The authors did not control for the use of tranquilizers which have repeatedly been shown to impair cognitive function.[204] The authors conducted the study from a biased perspective since it was assumed that opioids cause cognitive impairment, and the results are a reflection of the patients selected and methodology used.

Lorenz, Beck, and Bromm examined the effects of sustained release morphine (initial dose = 30mg) and experimentally induced pain in six female patients with chronic nonmalignant pain (mean VAS pain intensity score = 7.3, s.d. = +/- 2.3).[205] At follow-up, patients reported substantial reduction in pain (mean VAS pain intensity score = 2.7, s.d. = +/- 2.1), while objective measures of cognitive function showed no change or minor improvement. Long-term follow-up (> 1 year) showed that patients had substantially increased morphine doses, however pain was well controlled with few side-effects such as constipation and no problems associated with drowsiness and concentration. Experimentally induced pain did not affect cognitive ability. Patients reported an improved mood along with feeling less stressed and depressed. These results are consistent with the stages of pain model which suggests that pain suffering rather than intensity is correlated with cognitive impairment.

Haythornthwaite et al. evaluated the effect of long-acting opioid analgesics (methadone/SR-morphine) on cognitive function and depression.[206] Subjects (n=19) included chronic pain patients (pain that persisted longer than 6 months) that had not improved in response to standard therapy. The following assessments were made at baseline and follow-up: Multidimensional Pain Inventory (MPI), Symptom Checklist 90-R (SCL-90-R), Beck Depression Inventory (BDI), Grooved Pegboard test,

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[204] Coull JT, Sahakian BJ, Middleton HC, et al. Differential effects of clonidine, haloperidol, diazepam and tryptophan depletion on focused attention and attentional search. *Psychopharmacology*. 1995;121:222-230.

[205] Lorenz J, Beck H, Bromm B. Cogntive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. *Pain*. 1997;73:369-375.

[206] Haythornthwaite JA, Lynette MA, Quatrano-Piacentini Al, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *Journal of Pain and Symptom Management*. 1998;15:185-194.

Hopkins Verbal Learning Test (HVLT), the Trail Making Test (Part A), and the Digit Span subscale from the Wechsler Adult Intelligence Test – Revised (WAIS-R). In addition to the experimental group, a sample of 10 patients receiving standard care served as a control group for the study. Controls that utilized short-acting opioids on an as needed basis were put on a regular dosing pattern. Patients in the treatment group rated their pain to be significantly more ($p < 0.05$) severe (mean = 5.30) than control group patients (mean = 4.43) at baseline. An approximately equal proportion of patients in the treatment (79%, mean follow-up period –5.8 months) and control groups (80%, mean follow-up period – 3.0 months) reported using short acting opioids at baseline.

Mean improvement in pain severity was significantly greater for the group receiving long acting opioids (mean difference = -1.93) as compared to the usual care group (mean difference = -0.24) at the 95% level. While only two patients in the usual care group reported increased ability to participate in work and leisure activities, nine patients in the treatment group reported such an improvement. Although no significant differences were observed between depression levels for the two groups, mean reduction in anxiety (-0.27) and hostility (-0.20) were significantly different than the mean increase in scores (0.13 and 0.31 respectively) for the two scales among control group patients.[207]

Mean scores on the Digit Symbol (DS) test improved significantly [$F(1,25) = 5.3$, $P<0.05$] from baseline to follow up for the treatment group. As compared to usual care patients who showed a drop in scores for the DS test (mean decline = -1.1), long acting opioid users showed a significant improvement in the Digit Symbol test scores at follow-up (mean improvement = 4.4). No significant differences were observed on other cognitive function tests (grooved pegboard, Hopkins Verbal Learning Test, Trail Making Test- Part A&B, Digit Span Subscale) either between or

[207] Ibid

within groups at follow-up.[208] It can be speculated that more group differences would have emerged with a larger sample size.

The results indicated that reduction in pain severity was observed in patients responding to lower doses of long acting opioids. A larger sample size would have enabled robust conclusions about the comparative effects of short and long acting opioids on cognitive function. Follow-up period ranged from 3 to 5 months suggesting that the likelihood of improvement in cognitive test scores due to practice effects was minimal. The authors concluded that the improvement in performance on this cognitive test may be a function of the analgesic relief obtained due to the treatment.[209]

Francis examined the effect of opioid therapy on various aspects of cognitive functioning such as verbal learning and memory, short-term memory, visuomotor tracking, psychomotor speed and accuracy, and sustained attention.[210] Pain intensity, depression, and opioid medications (hydrocodone, propoxyphene, and codeine) were considered as independent variables. Pain intensity was assessed using a 11-point rating scale, and the Beck Depression Inventory was used to assess depression among patients. Scores on all tests were obtained at baseline (when patients began treatment with opioids) and one month after opioid dose had been stabilized. The results were analyzed by calculating change scores for each independent variable and cognitive function test score. A regression equation was developed for each test with change in cognitive function test score as the dependent variable.

The California verbal Learning Test (CLVT) was used to measure verbal memory and included eight subtests. Results from a t-test showed that scores on a total of six subtests (List A Trial 5, List B, Short Delay Free, Short Delay Cued, Long Delay Free, Long Delay Cued) improved significantly at follow-up. However, only the regression model with List A Trial 1 subtest as the dependent measure was

[208] Ibid
[209] Ibid
[210] Francis SE. The effects of long term opioid therapy on neuropsychological functioning in chronic pain patients. California Institue of Integral Studies. Dissertation. June 1999; 130p.

significant. Only the BDI accounted for a significant proportion of the variance (sr^2 = 0.166, $p < 0.01$) in test score change.

The Digit Span Forward and Backward is a measure of short term memory. Scores on the digit forward test declined (mean change = -0.22, $p > 0.05$),while scores on the digit backward improved (mean change = +0.22, $p > 0.05$). The regression model showed that pain and opioid dose accounted for a significant proportion of the variance in the digit forward test. Higher pain scores correlated with higher scored on the digit forward test, a result that was contrary to that hypothesized. Larger opioid doses were associated lower scores on the test.

The Trailmaking tests Part A and B are a measure visuomotor tracking and complex attention. A significant improvement in scores was observed for both Part A (mean change = -6.95, sd = 11.49, $p < 0.001$) and Part B (mean change = -13.55, sd = 42.19, $p < 0.05$). None of the independent variables accounted for the variance in these measures.

The grooved pegboard test is a measure of psychomotor function and utilizes the dominant and non dominant hands to assess function. The mean test scores at follow-up for the dominant hand improved and were significantly different from baseline (mean change = -5.12, sd = 10.89, $p < 0.01$). Pain intensity, depression, and opioid dose did not account for any variance in psychomotor function.

The Continuous Performance Test (CPT) is a measure of sustained attention that incorporates five subtests. None of the subtests showed a significant change in score from baseline to follow-up, and only depression accounted for 20 percent of the variance in the CPT Hit Reaction Time Standard Error ($p < 0.01$) and 24 percent of the variance in the CPT variability subtest.

Results from this study indicate that short-acting narcotic analgesics have minimal effects on cognitive function. Patients were only prescribed short acting opioid agents such as hydrocodone, codeine, and propoxyphene. Cognitive impairment is of greater importance in patients that are prescribed long-acting opioid agents. As patients are maintained on a constant dose, their ability to focus at work,

drive, and participate in other activities is often questioned. A related limitation with the previous study is the time of testing. Often short-acting opioids produce deleterious effects within two hours of administration and the variability in dose may produce results that can be misleading.[211]

Sjogren et al. prospectively studied 40 chronic pain patients that had been stabilized on opioid therapy for at least two weeks.[212] The following drugs were included in the study sustained release morphine (n = 23), methadone (n = 12), ketobemidone (n = 2), buprenorphine (n = 2), and tramadol (n = 1). All doses were converted into an equianalgesic morphine dose, and median morphine dose used was 60 mg. Evaluations on neuropsychological tests (CRT, FTT, PASAT) were compared with a matched control group.

On the CRT test, a significantly (p = 0.022) slower reaction time was observed for patients than controls that had scores in the lowest percentile. As compared to controls, patients performed poorly on the FTT [dominant hand (p = 0.008) and nondominant hand (p = 0.003)], as well as on the PASAT (p less than or equal to 0.02). Anxiety and depression measures did not correlate with test scores.

The authors concluded that treatment with long-term opioids negatively affects cognitive ability in nonmalignant pain patients as compared to a normal population. Since this study utilized a cross-sectional design, it is not possible to ascertain if patient condition had improved at all on opioid therapy. The median age of patients and controls was 60 and 59 years respectively. Patient characteristics such as age and extent of distress due to pain may have contributed to differences in cognitive abilities that were observed between the two groups. The biggest drawback of this study is the utilization of a control group that is healthy as opposed to pain patients with similar characteristics that are not taking opioid medications. Consequently, the

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[211] Saarilho-Kere U, Julkunem H, Mattilla J et al. Cited by: Chapman SL, Byas-Smith MG, Reed BA. Effects of intermediate and long term use of opioids on cognition in patients with chronic pain. *The Clinical Journal of Pain*. 2002;18:583-590.

[212] Sjogren P, Thomsen AB, Olsen AK. Impaired neuropsychological performancein chronic nonmalignant pain patients receiving long-term oral opioid therapy. *Journal of Pain and Symptom Mangement.* 2000;19:100-108.

interpretation of these results in the context of a chronic nonmalignant pain patient population is limited. A measure of performance prior to opioid use would have provided insight into the potential effects of pain on cognitive performance.

Driving is an important daily activity that pain patients on opioid therapy must be capable of performing in order to achieve a sense of return to normal function. In a comparison of driving ability tested by means of a simulator, patients on chronic opioid analgesic therapy (COAT) performed significantly better than age matched cerebrally compromised patients (cerebrovascular accidents, traumatic brain injury, and anoxia). Although COAT patients made errors on tasks that required speed and accuracy, the authors attributed the errors to hasty actions rather than impairment caused by drugs.

1.3.16 Effects of Opioids on Cognitive Function in Patients with Cancer Pain

Opiods are often used in the management of pain in cancer patients. "The specific contribution of opioids to the cognitive impairment associated with advanced cancer is often difficult to evaluate owing to the frequent presence of multisystem impairment and the concurrent administration of other psychotropic medications."[213] Characteristics such as disease severity, complications, and numerous medications associated with cancer can individually and collectively affect cognitive status. Additionally, a large proportion (60%) of cancer patients belong to the older age group (age ≥ 65). These patients are particularly prone to experiencing pain, and cognitive functioning normally declines in elderly patients. Thus, studies evaluating cognitive deficits due to opioids in the cancer population are plagued by numerous confounding variables.

Results from thee studies that utilized Continuous Reaction Time to examine the cognitive effects of opioids in cancer patients showed that test times were prolonged in groups that received the drug. Opioid-naïve patients were more likely to exhibit delayed reaction times than those patients that had been stabilized on a dose.[214] Findings from this population cannot, however, be extended to other groups of patients experiencing pain of nonmalignant origin. Multiple reasons, including susceptibility to cognitive dysfunction, older age, and numerous other disease-related factors prevent the extrapolation of these results.

Results of studies evaluating the effects of opioids on neuropsychological functioning must be interpreted taking into consideration factors such as dose variations, opioid type and route, frequency of dosing, and interval between administration of dose and neuropsychological testing.

Sjogren and colleagues assessed the effects of opioids, performance status, and pain on some facets of neuropsychological function in cancer pain patients (n =

[213] Lawlor PG. The Panorama of opioid-related cognitive dysfunction in patients with cancer: a critical literature appraisal. *Cancer*. 2002;94:1836-1853.
[214] Ibid.

130).[215] Potential confounding medications such as benzodiazepines, antidepressants, anticonvulsants, neuroleptics, etc were excluded from the trial. Patient reported pain (no pain and intolerable pain were anchors) and sedation (quite alert and extremely tired were anchors) levels were obtained on a VAS. The following tests were administered about 150 minutes after administration of morphine doses: continuous reaction time (CRT) which measures vigilance, finger tapping test (FTT), and paced auditory serial addition task (PASAT) which is associated with memory function.

Patients in the control group (n = 40) [karnofsky performance status (KPS) A] experienced no pain and did not receive opioids. Their scores on the psychomotor tests were not statistically different from matched healthy controls. Comparisons were drawn between the control group and 4 other groups. Group 2 (n = 19) – KPS B, no pain, no opioids; Group 3 (n - 19) – KPS B pain no opioids; Group 4a (n = 31) - KPS B, pain, opiods administered (average dose = 120 mg); Group 4b (n = 21) – no pain, opioid administered (average dose = 40mg).

As compared to other groups, patients in group 4a had the lowest score on all tests. As compared to patients in the control group, patients in all groups except 3 had significantly ($p < 0.05$) slower scores on the CRT test. Performance on the FTT was significantly ($p < 0.01$) slower by patients in group 3 and 4a than patients in the control group. Average scores on PASAT were significantly better for patients in group 4b versus group 4a, suggesting that pain may mediate working memory. However, since group 2 and 3 did not differ statistically, this conclusion may be erroneous especially among patients not treated with opioids. Pooling data from the two opioid treated groups and untreated groups showed no differences on PASAT test scores, while combining groups with pain free patients (2 and 4b) and those still experiencing pain (3 and 4a) showed significantly better scores for the pain-free group.

Since patients receiving opioids had been stabilized on their doses for two weeks, the results suggest that long-term opioid use does not significantly affect

[215] Sjogren P, Olsen AK, Thomsen AB, Dalberg J. Neuropsychological performance in cancer patients; the role of oral opioids, pain and performance status. *Pain.* 2000;86:237-245.

scores on cognitive function tests. Cognitive tests were administered shortly after dose administration. A spike in blood drug levels may have caused some side-effects such as drowsiness, thereby confounding the results of these tests. The results indicate that pain may mediate cognitive ability.

Clinicians that treat cancer patients with long-term opioid therapy have reported positive outcomes with this management strategy. Contrary to expectations about adverse effects, problems such as sedation and cognitive impairment are not typically observed.[216]

The above literature has demonstrated that pain does impair neuropsychological functioning. A number of factors such as anxiety, sleep disturbances, depression, and medication (opioid & benzodiazepine) use in pain patients contribute to abnormal cognitive functioning. Results from various studies indicate that aspects of attention, memory, speed of processing, and executive control functions may often be disrupted due to chronic pain that is untreated/under treated.[217] Treatment of the underlying pain would probably alleviate these problems, and restore homeostasis.

[216] Galski T, Williams JB, Ehle HT. Effects of opioids on driving ability. *Journal of Pain and Symptom Management.* 2000;19:200-208.
[217] Nicholson K, Martelli MF, Zasler ND. Does pain confound interpretation of neuropsychological test results? *NeuroRehabilitation.* 2001;16:225-230.

Chapter 2: Study Objectives and Theoretical Framework

In this chapter, a statement of study objectives will be made. The study objectives and observations from the literature review will serve as guide to develop the theoretical rationale for the study.

The stages of pain model (figure 2.1), which was developed in the 1990's will be used as the underlying theoretical basis for the study. The association between stages of pain model variables, exogenous variables (age, gender, and ethnicity), and endogenous variables (narcotic analgesic dose and benzodiazepine dose) will be discussed.

A path analytic framework will be used to model the relationships between the variables discussed above and measures of attention (digit span test, digit symbol test, and the paced auditory serial addition test), which will serve as the dependent variables. A separate model for each dependent variable will be constructed. Finally, hypothesis based on the modeled relationships will be proposed for each model.

2.1 Study Objectives

1. The primary purpose of this study is to examine the association between Avinza® and performance on neuropsychological tests in chronic non-malignant pain patients while controlling for other variables such as pain intensity, pain unpleasantness, pain suffering, pain behaviors, and benzodiazepine use. More specifically, measures of attention associated with immediate recall (*digit span forwards and backwards*), sustained attention and information processing (*PASAT*), visual attention and motor persistence (*digit symbol subtest of the WAIS-R*) will be evaluated.

2. To examine the association between benzodiazepine dose and performance on tests of cognitive function.

3. To examine whether pain intensity and unpleasantness have an indirect influence on measures of attention mediated by pain suffering and pain behaviors.

4. To determine whether adequate pain control with Avinza influences the direct association between pain suffering and performance on tests of cognitive function.

5. To determine whether adequate pain control with Avinza influences the direct association between pain behaviors and performance on tests of cognitive function.

2.2 Theoretical Framework for Study

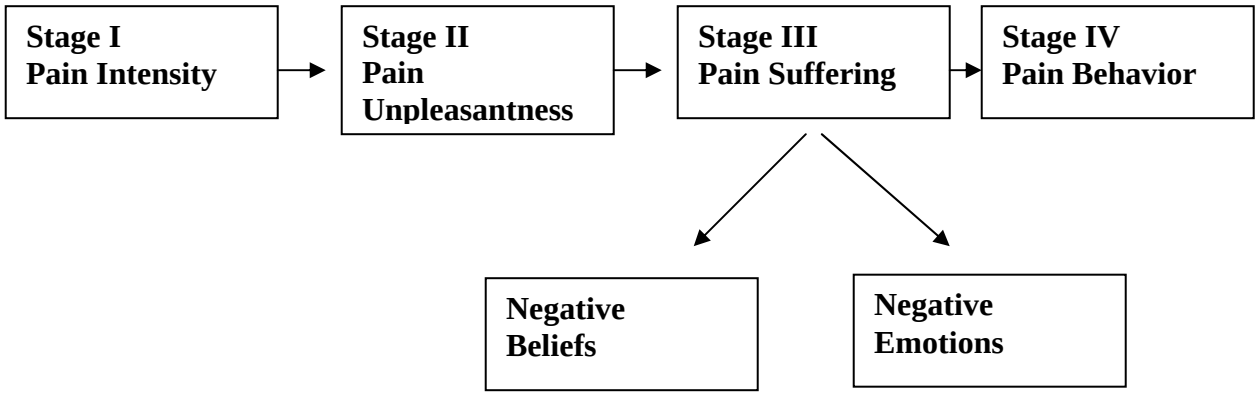
The stages of pain model will serve as the theoretical basis for this study. The rationale for using the stages of pain model will be discussed below.

2.2.1 Stages of Pain Model

The sensory, affective, and cognitive dimensions of pain proposed in the Gate Control Theory (GCT) have been further evaluated and are believed to be composed of sub-parts that coincide with various stages of pain processing.[218]

Wade et al. have proposed a four-stage model of pain process. The following figure presents an illustration of the model:[219]

Figure 2.1 Stages of Pain Model



[218] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain*. 1996;68:157-167.
[219] Wade JB, Hart RP. Attention and the stages of pain processing. *Pain Medicine.* 2002;3:30-38.

"A theoretical scheme of dimensions and stages of pain may be useful in identifying the level at which therapeutic interventions exert their influence."[220] Wade and colleagues applied a linear structural relations (LISREL) approach to identify the structural relationship between the four pain stages, assess validity of latent constructs, and examine the predictive ability of the model.[221] Pain intensity and unpleasantness were measured on a VAS with the following anchors: "no sensation" and "the most intense sensation imaginable", and "not bad at all" and "the most intense bad feeling imaginable", respectively. Pain affect (emotional distress, i.e., depression, anxiety, frustration, fear, anger) and perception of impact on life (beliefs about interference with participation in desired activity, difficulty in enduring pain, ability to reduce pain, and likelihood of cure) were measured as indicators of stage 3 processing. Pain-related behavior was measured by utilizing five items from the psychological pain inventory. Best fit was obtained after the dimension about "impact of pain on life" was dropped from the model. A weak relationship was found between suffering and behavior. The authors attributed the weak association to differences in measurement, i.e, visual analogue scales for all other items versus multiple rating methods for behavior items. Previous research has demonstrated that factors such as gender, age, and type of pain disorder do not significantly influence the modeled variables.[222]

In a recent study, the stages of pain model served as a heuristic to examine the association between chronic pain and cognitive function. In order to assess cognitive function, the Digit Span (D.S.) test, which is a measure of immediate recall was used. The results from stepwise regression analysis indicated that depressed mood ($r^2 = 0.04$, $p < 0.0001$), interference due to pain ($r^2 = 0.03$, $p < 0.0001$), and "solicitous behavior and change in daily activities" ($r^2 = 0.04$, $p < 0.0001$) accounted for significant variance in attentional performance.

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[220] Ibid.
[221] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain.* 1996;68:157-167.
[222] Wade JB, Dougherty LM, Hart RP, Rafii A, Price DD. A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behavior. *Pain.* 1992;51:67-73.

Wade and Hart suggest that follow-up studies utilizing the stages of pain model should utilize multiple measures of attention, working memory capacity, and information processing speed to gauge the association between cognitive function and chronic pain.[223] Thus, the purpose of this study is to evaluate the association between long-acting morphine (Avinza®), and performance on neuropsychological tests assessing short-term memory, information processing, and motor skills in chronic pain patients, while controlling for stages of pain model variables and the effects of benzodiazepines.

2.3 Key Model Variables

A detailed description of each variable included in the proposed study model, and the modeled relationships shall be examined below. The ensuing discussion first presents a description of the stages of pain model variables. This is followed by examining the association between demographic variables, medication use and the stages of pain model variables,

2.3.1 Stage I

The concept of stages of pain processing was introduced in the 1980s. It is believed that pain perception can be characterized by four stages that are distinguishable in chronic pain patients.[224] The first stage is described as pain intensity, which is indicative of responsiveness to nociceptive stimuli. Visual analog scales (VAS), "verbal descriptor scaling methods," and "other cross modality matching methods" have been used to measure perceived pain intensity.[225] It is hypothesized that pain intensity does not influence attention directly, but the relationship is mediated through pain unpleasantness, pain suffering, and pain behaviors.

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[223] Wade JB, Hart RP. Attention and the stages of pain processing. *Pain Medicine.* 2002;3:30-38.
[224] Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain*. 1989;36:209-218.
[225] Wade JB, Dougherty LM, Hart Rp, Rafii A, Price DD. A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behavior. *Pain*. 1992;51:67-73.

2.3.2 Stage II

The second stage of pain experience known as pain affect (unpleasantness) has been measured using sound psychometric theory.[226] It is characterized by the continuous sensations of unpleasantness that are evoked in the presence of painful stimuli.[227] Pain affect correlates closely with pain intensity, and is moderately associated with cognitive processing. Pain affect has been validated by measuring response to both experimentally induced and clinical pain. Pain affect, like pain intensity is measured with VAS; however, ratings have been demonstrated to measure different dimensions.[228] Pain affect is also referred to as "Stage 1 affect."[229] Subjects who are exposed to experimental pain typically provide higher pain intensity ratings and lower pain affect ratings, while the opposite trend is observed in chronic pain populations. This is indicative of the lack of concern for harmful or negative outcomes associated with experimental pain. Pain intensity is independent of psychological factors that influence pain affect.[230]

Neurophysiological findings also indicate that perceived unpleasantness and affect due to noxious stimuli are associated with excitatory activity in a different region of the brain, namely the anterior cingulated cortex (ACC) and pain intensity is linked to activity in the primary somatosensory cortex. Rainviille and Duncan concluded that the ACC is the most critical determinant in the perception of pain unpleasantness; however, various structures such as the somatosensory cortex, ACC, and PAG which are responsible for "encoding different aspects of pain" are

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[226] Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain*. 1989;36:209-218.
[227] Wade JB, Dougherty LM, Hart Rp, Rafii A, Price DD. A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behavior. *Pain*. 1992;51:67-73.
[228] Price DD, et al. Cited by: Wade JB, Price DD, Hamer RM, Schwartz SM, Hart RP. An emotional component analysis of chronic pain. *Pain*. 1990;40:303-310.
[229] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain*. 1996;68:157-167.
[230] Wade JB, Dougherty LM, Hart RP, Rafii A, Price DD. A canonical correlation analysis of the influence of neuroticism and extraversion on chronic pain, suffering, and pain behavior. *Pain*. 1992;51:67-73.

associated and "highly interactive."[231] These physical findings clearly substantiate the existence of two different stages in the perceptions of pain. Rainville and colleagues have also demonstrated this difference experimentally through the use of hypnosis.[232]

According to Price and colleagues, pain that poses a threat to life or health (i.e., cancer pain, chronic pain) would influence affective ratings of pain to a greater extent than pain that is characterized as being less harmful (e.g., labor pain).[233] Cancer, causalgia, upper back pain and low back pain patients provided significantly ($p < 0.05$) higher affective pain ratings than sensory pain ratings, while labor pain patients provided significantly ($p < 0.05$) higher pain intensity ratings. Labor pain patients who focused more on the pain than on the impending birth tended to provide higher affective ratings, thus lending further support to the hypothesis. Various psychological and cognitive factors such as impact of pain on daily activities and future health, and perceived locus of control influence pain affect. Differentiation between various pain ratings for various groups of pain patients can provide a sound basis for assessing the effects of different therapeutic strategies. Both, pain intensity and pain unpleasantness are believed to influence measures of attention indirectly through pain suffering (stage III) and pain behaviors (stage (IV).

2.3.3 Stage III

The third stage of pain experience (Stage 2 affect) is an expression of individual beliefs, mood and emotional distress. Individual beliefs stem from past experiences and perceptions about the future. Individuals have variable responses to their condition; some patients are significantly hampered by their pain while others prevent pain from disrupting their lifestyle. Patients in whom symptoms flare or do not

[231] Rainville P, Duncan GH. Pain affect encoded in human anterior cingulated but not somatosensory cortex. *Science*. 1997;277:968-971.
[232] Rainville P, Carrier B, Hofbauer RK, Bushnell MC, Duncan GH. Dissociation of sensory and affective dimensions of pain using hypnotic modulation. *Pain*. 1999;82:159-171.
[233] Price DD, Harkins SW, Baker C. Sensory-affective relationships among different types of clinical and experimental pain. *Pain*. 1987;28:297-307.

subside form references to previous experiences associated with their pain. Additionally, patients can vary in their outlook about the potential consequences of chronic pain, which may either be realistic or exaggerated. These evaluations contribute to pain suffering. Negative evaluations about pain are expected to give rise to a variety of negative emotions. Experiences with pain and its impact on lifestyle influence cognitive processes, which give rise to a variety of emotional responses. Accordingly, the third stage of pain processing has been referred to as suffering. Pain experienced long after an injury has healed would remind an accident victim about the mishap and subsequent suffering.[234]

Wade and colleagues suggested that the emotional component of pain includes negative emotions such as fear, anxiety, frustration, and anger in addition to depression.[235] Five visual analog rating scales describing each emotion were correlated with pain affect scores (pain unpleasantness –maximum, minimum, and usual) and depression scores obtained through the Beck Depression Inventory (BDI) and the depression scale of the Minnesota Multiphasic Personality Inventory (MMPI). A canonical correlation analysis indicated that negative emotions explained 11 percent of the variance in pain unpleasantness (correlation was significant only for maximum pain unpleasantness) and 33 percent of the variance in BDI scores. A multiple regression analysis showed that anxiety and frustration predicted maximum pain unpleasantness; anxiety, frustration and anger predicted minimum pain unpleasantness; and only frustration predicted usual levels of pain unpleasantness. Depression and anger contributed significantly to BDI scores. It was interesting to note that none of the pain unpleasantness levels were predicted by depression ratings. These findings lend support to the hypothesis that pain unpleasantness and pain suffering are separate dimensions. It can be argued that pain patients who are frustrated with their condition experience an increase in pain unpleasantness levels, which leads to psychological distress and depression. Although the five VAS ratings

[234] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain.* 1996;68:157-167.
[235] Wade JB, Price DD, Hamer RM, Schwartz SM, Hart RP. An emotional component analysis of chronic pain. *Pain.* 1990;40:303-310.

correlated with the BDI, the authors suggest that these measures should not be used to substitute the BDI, which is a more reliable assessment of depression among pain patients.

Depression is commonly prevalent among patients with chronic pain. Reports about the incidence of depression in chronic pain vary tremendously ranging from 10 percent to 90 percent.[236,237] The large discrepancy may be attributable to the variability in criteria used to assess depression in chronic pain.[238]

Both pain and depression are separate, yet related normal physiologic responses designed to conserve energy and enable survival in the face of internal or external threats. Depressive symptoms are linked to cytokines, which regulate the function of the immune system. The depressive symptoms include "behavioral (restlessness, reduced activity, hypersomnia, social withdrawal), cognitive (lack of concentration, loss of interest), and affective (depressed mood, anhedonia) components," which "represent a motivational state that promotes resistance to pathogens by resetting an organism's priorities." In some situations, improper regulation of these mechanisms may result in motivational states that are repetitive and persistent. Like depression, pain is a motivational process. The involvement of the immune system and the inability to self-regulate cytokine mechanisms lead to the development of chronic syndromes.

2.3.4 Stage IV

According to Loeser and Egan, behavior is the only observable aspect of these different stages of pain.[239] Pain behavior can be measured either through self-reports or proxy reports, or by means of observation. Inability or limited ability to work, partake in social and recreational activities, and perform daily tasks due to pain

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[236] Hendler N. Depression caused by chronic pain. *Journal of Clinical Psychiatry*. 1984;45:30-36.
[237] Lindsay PG and Wyckoff M. The depression-pain syndrome and its response to antidepressants. *Psychosomatics. 1981*;22:571-577.
[238] Gallagher RM, Moore P, Chernoff I. The reliability of depression diagnosis in chronic low back pain. *General Hospital Psychiatry*. 1995;17:399-413.
[239] Loeser JD, Egan KJ. History and organization of the university of Washington multidisciplinary pain center. In: Loeser JD, Egan KJ (Eds.). Managing the chronic pain patient, Raven Press. New York, 1989.

constitute the construct of pain behavior. It can be hypothesized that patients with high levels of self-efficacy exhibit positive behaviors and beliefs about their condition, which may be associated with improved outcomes.

Factors such as fear about pain and the degree to which pain can be controlled, or the lack of control contribute largely to anxiety, perception about increased pain intensity, and a requirement for excess medications. Patients who have negative appraisals about their condition also limit their activities drastically to the extent that they become disabled.[240]

Avoidance of certain activities can lead to anticipatory perceptions about other activities that can potentially evoke pain, thereby causing anxiety. Perceptions about illness and health are learned. Pain is always accompanied by discomfort or unhappiness and is, therefore, inherently an emotional experience. It has been estimated that 50 percent of chronic pain sufferers are depressed. Lack of control and inability to partake in activity can contribute to depression. Anger can contribute to perceived interference, pain intensity, and frequency of pain behaviors. "The cognitive activity of chronic pain patients may contribute to the exacerbations, attenuation, or maintenance of pain, pain behavior, affective distress, and dysfunctional adjustment to chronic pain."[241] In addition to pain intensity, emotional disturbances as well as disruption of day to day activities may contribute to attention disruption in pain patients.

A sub-objective of this study will be to validate the factor analytic structure of the stages of pain model. Thus, the variables used to develop the constructs (pain intensity, pain unpleasantness, pain suffering, and pain behaviors) will be measured using the same instruments utilized by Wade and colleagues.[242] In order to validate the pain suffering construct, a multiple regression analysis will be performed by regressing BDI scores on the observed variables used to form the construct.

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[240] Bond MR. Psychological issues in cancer and non-cancer conditions. *Acta Anaesthesiologica Scandanavica*. 2001;45:1095-1099.
[241] Ibid.
[242] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain*. 1996;68:157-167.

2.3.5 Narcotic Analgesics

It is hypothesized that pain intensity is predictive of narcotic dose; high pain intensity is positively correlated with a greater average daily narcotic dose. In this study, patients with uncontrolled pain on short-acting narcotics will be initiated on Avinza®, a long-acting morphine agent. Opioid rotation whereby patients are switched to a more potent opioid is a strategy employed to overcome lack of analgesia or intolerable side-effects including cognitive dysfunction. Opioid switches require the calculation of equianalgesic dose ratios. "An equianalgesic dose refers to a dose that yields roughly equivalent analgesia to the standard set in a given equianalgesic dose table."[243] Dose selection depends on the previous dose of the patient's narcotic analgesic, relative potency of the drug being initiated, and characteristics of the opioid being discontinued. In a study of cancer patients, similar dose ratios were required for rotation from morphine to methadone in both neuropathic and non-neuropathic pain patients.[244] Although there is no defined upper extremity with regard to opioid dosing in the control of pain,[245] most patients will be initiated on the lowest available Avinza dose (30mg).

The published literature reviewed in the previous section demonstrated a weak association between narcotic use and impaired attention among pain patients. Thus, it is hypothesized that the correlation between narcotic dose and tests of attention is low.

2.3.6 Benzodiazepines

Benzodiazepines are commonly prescribed in the management of chronic pain.[246] Often, chronic pain patients experience insomnia and benzodiazepines are useful in inducing sleep. It is well documented that anxiety is highly prevalent in the population

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[243] Anderson R, Saiers JH, Abram S, Schlischt C. Accuracy in equianalgesic dosing: conversion dilemmas. *Journal of Pain and Symptom Management.* 2001;21:397-406.
[244] Gagnon B, Bruera E. Differences in the ratios of morphine to methadone in patients with neuropathic pain versus non-neuropathic pain. *Journal of Pain and Symptom Management*. 1999;18:120-125.
[245] Anderson R, Saiers JH, Abram S, Schlischt C. Accuracy in equianalgesic dosing: conversion dilemmas. *Journal of Pain and Symptom Management.* 2001;21:397-406.
[246] King SA, Strain JJ. Benzodiazepine use by chronic pain patients. *The Clinical Journal of Pain.* 1990;6:143-147.

of chronic pain patients. Further, anxiety is linked with other emotional symptoms such as depression, anger, frustration, and sleep disturbances. Thus, benzodiazepines are prescribed to treat anxiety, or in conditions where anxiety is not a prominent symptom, their muscle relaxant properties could serve to provide analgesic relief.[247] Despite these benefits, the use of benzodiazepines is associated with many disadvantages.

According to Breggin, benzodiazepines have several toxic effects such as, sedation, hypnosis, cognitive dysfunction, agitation, anxiety, and other behavioral aberrations.[248] Benzodiazepines produce changes in normal behavior through two different modes of action. Direct intoxication results in "impaired executive and cognitive function, including reduced judgment and impulse control.[249]" Withdrawal of the drug or loss in efficacy results in rebound symptoms, which are responsible for emotional outbursts. Long-term users of benzodiazepines have impaired performance on tests of sustained attention.[250] Recently, benzodiazepine use has been linked with anterograde amnesia. Subjects administered midazolam showed an impaired ability to learn; a dose-dependent association was found between benzodiazepines and activity in regions of the brain association with information processing and memory.[251]

Studies assessing the effects of benzodiazepines on cognitive function have showed that test scores often improve after withdrawal of benzodiazepines irrespective of duration of use. These results further support the conclusion of a dose-response association between benzodiazepine use and performance on tests of cognitive function.[252,253]

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[247] Dellemijn PL, Fields HL. Do benzodiazepines have a role in chronic pain management. *Pain.* 1994;57:137-152.

[248] Breggin PR. Brain-disabling treatments in psychiatry: drugs, electroshock and the role of the FDA. Springer Publishing Company. 1997. New York, NY.

[249] Ibid.

[250] Golombok S, Moodley P, Lader M. Cognitve impairment in long-term benzodiazepine users. *Psychological Medicine*. 1988;18:365-74.

[251] Reinsel RA, Veselis RA, Dnistrian Am et al. Midazolam increases cerebral blood flow in the left prefrontal cortex in a dose-dependent fashion. *The International Journal of NeuroPsychopharmacology.* 2000;3:117-127.

[252] Scheman J, Aker R, Covington E. Cognitive effects of opioid and benzodiazepine weaning. Abstract. *American Pain Society*. 2003;Poster# 859. http://www.ampainsoc.org/abstract/2003/data/859/index.html. Accessed:Jun 11, 2003.

[253] Curran KC, Marks HN, Basoglu M. Long-term effects of alprazolam on memory: a 3.5 year follow-up of agrophobia/panic patients. Pschological Medicine. 1999;29:225-231.

Thus in assessing the effects of long-acting narcotic agents on cognitive impairment in chronic pain, the ideal research design would exclude all patients on benzodiazepines. However, numerous chronic non-malignant pain patients in clinical practice are maintained on benzodiazepines. Eliminating these patients from the study would significantly limit the sample. Therefore, benzodiazepine dose is included in the model as a control variable. The effects of benzodiazepine on cognitive impairment will be controlled for statistically in the study model.

2.3.7 Association between Exogenous Variables and Stages of Pain Model

2.3.7.1 Ethnicity

Previous studies have documented differences among various racial/ethnic groups about the meaning of pain to life and beliefs about pain and the ability to control it.[254] Results from one study indicated a tendency among African-American and Italian patients to blame themselves for their condition.[255] As compared to Whites, African Americans viewed being in pain as analogous to being ill. The belief that pain is self-inflicted or a perception that magnifies the potential consequences of pain tend to be associated with pain-related fear and depression.[256]

More recently, the association between race/ethnicity and the chronic pain experience has been examined in the context of the stages of pain model. Riley and colleagues used structural equation modeling techniques to examine differences between White (n = 1084) and African-American (n = 473) chronic pain patients across the model variables.[257] African American chronic pain patients on average provided significantly higher usual pain unpleasantness levels [5.2 (s.d. = 0.07) vs 4.7

[254] Bates MS, Rankin-Hill L. Control, culture, and chronic pain. *Social Science and Medicine*. 1994;39:629-645.
[255] Lipton JA, Marbach JJ. Ethnicity and the pain experience. *Social Science and Medicine*. 1984;19:1279-1298.
[256] Jordan MS, Lumley MA, Leisen JC. The relationships of cognitive coping and pain control beliefs to pain and adjustment among African-American and Caucasian women with rheumatoid arthritis. *Arthritis Care and Research.* 1998;11:80-88.
[257] Riley JL, Wade JB, Myers CD, Sheffield D, Papas RK, Price DD. Racial/ethnic differences in the experience of chronic pain. *Pain*. 2002;100:291-298.

(s.d.=0.11)], negative emotion ratings [19.6 (s.d. = 0.51) vs 17.3 (s.d.= 0.34)], and pain behavior ratings [19.3 (s.d. = 0.58) vs 17.7(s.d.=0.38)] compared to whites. A mean difference of 1.0 on a VAS was considered clinically significant. Education and duration of pain were included as control variables. The two groups were compared by relaxing the constraints between successive stages of the model one at a time. The two groups differed primarily on pain suffering and its association with pain behaviors, with African Americans demonstrating a stronger link between these two stages. These results indicate that interventions focusing on management of emotional distress are more likely to benefit African Americans. Depression and other factors that constitute pain suffering may limit activity in these patients due to lethargy, fatigue, and reduced motivation levels.

2.3.7.2 Age

There is little knowledge about the association between age and pain, adaptation to pain, and response to therapy. The chronic nature of pain, the aging population and the large number of elderly that experience pain necessitate the delineation of these associations. Riley, Wade, and colleagues examined whether variations in pain processing are related to differences in age.[258] Chronic pain patients were categorized into three groups: younger adults (age – 18 to 44, n = 820); middle-aged adults (age 45-64, n = 596); and older adults (age ≥ 65, n = 159). Duration of pain did not correlate significantly with any of the stages of pain model variables. Univariate analysis indicated that all three age groups provided similar ratings for pain intensity and unpleasantness, however, older adults exhibited lower ratings of negative emotion and manifested fewer pain behaviors than the other two age groups. Structural equation modeling results showed a variation in the linear association between pain-related emotion and behavior across age categories. Older adults were least likely to exhibit pain behaviors and experience the lowest levels of emotional

[258] Riley JL, Wade JB, Robinson ME, Price DD. The stages of pain processing across the adult life span. *The Journal of Pain*. 2000;2:162-170.

suffering in response to pain. Middle-aged adults exhibited the highest levels of emotional distress, which was also manifest as behavior. The authors reasoned that middle-age adults provided the highest negative emotion ratings and displayed pain related behaviors to a greater extent as they were entering a phase of their life where health begins to deterioration and this phase of their life was compounded by the chronic pain condition. Younger adults are also more likely to experience greater distress and are more likely to report illness behavior due to the inability to perform routine activities.

2.3.7.3 Gender

Riley and colleagues examined the association between gender and various emotions such as anxiety, depression, fear, anger, and frustration in the context of the first three stages of pain model. Although women tended to provide higher pain intensity and unpleasant ratings than men, univariate analysis indicated no sex differences in ratings for depression, anxiety, and anger. A stronger association was found in the linear association between pain unpleasantness and pain emotions for males than females. However, these results do not indicate group differences for pain suffering. In the context of the present study model, these findings suggest that analgesic relief would be more predictive of lower ratings in pain unpleasantness, and therefore, pain suffering among males than among females. Thus, the relationship between gender and pain suffering is mediated by pain unpleasantness.

2.3.8 Dependent Variables – Measures of Attention

Measures of the dependent variable were selected to assess various aspects of an individual's ability to maintain attention. Several factors were considered in selecting these measures of attention: domain of attention being assessed, reliability, cost, ease of administration and scoring, sensitivity in a chronic non-malignant pain patient population.

2.3.8.1 Digit Span and Digit Symbol Subtest of the Wechsler Adult Intelligence Scale –III (WAIS-III)

The digit span subtest includes two tests, the digits forward and backward tests. The former is a measure of immediate recall and the latter is a measure of temporal ordering. These measures have fairly high reliability scores (0.66 to 0.89) and can be administered in a relatively short duration of time (4 to 6 minutes). The digit span test was sensitive to measures of stage III and IV of the stages of pain model.[259] The digit span test was included as part of this study to replicate these findings.

The digit symbol test assesses a wide range of cognitive abilities including motor persistence, sustained attention, response speed, and visuomotor attention. Motor function is an important aspect of daily functioning. The test-retest reliability of the digit symbol test is high (0.82 to 0.88). The test is easy to score and takes very little time to complete (90 seconds). Motor function in pain patients is impaired compared to healthy controls.[260,261] Abuse and dependence on opioids and tranquilizers was associated with poor performance on the digit symbol test.[262] Performance on digit symbol test did not deteriorate with long-acting narcotic use.[263] The digit symbol test will be included in this study since it is sensitive to the factors being studied. Both the digit span and digit symbol subtest are part of the WAIS-III making their use cost-effective.

2.3.8.2 Paced Auditory Serial Attention Test (PASAT)

The paced auditory serial attention test is a measure of information processing, and sustained attention. The test is highly reliable (0.9) and validity has been

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[259] Wade JB, Hart RP. Attention and the stages of pain processing. *Pain Medicine.* 2002;3:30-38.
[260] Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression, and healthy controls. *The Journal of Rheumatology*. 1995;22:137-142.
[261] Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology*. 1999;21:477-487.
[262] McNairy SL, Maruta T, Ivnik RJ, Swanson DW, Ilstrup DM. Prescription medication dependence and neuropsychologic function. Pain. 1984;18:169-177.
[263] Haythornthwaite JA, Lynette MA, Quatrano-Piacentini Al, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *Journal of Pain and Symptom Management*. 1998;15:185-194.

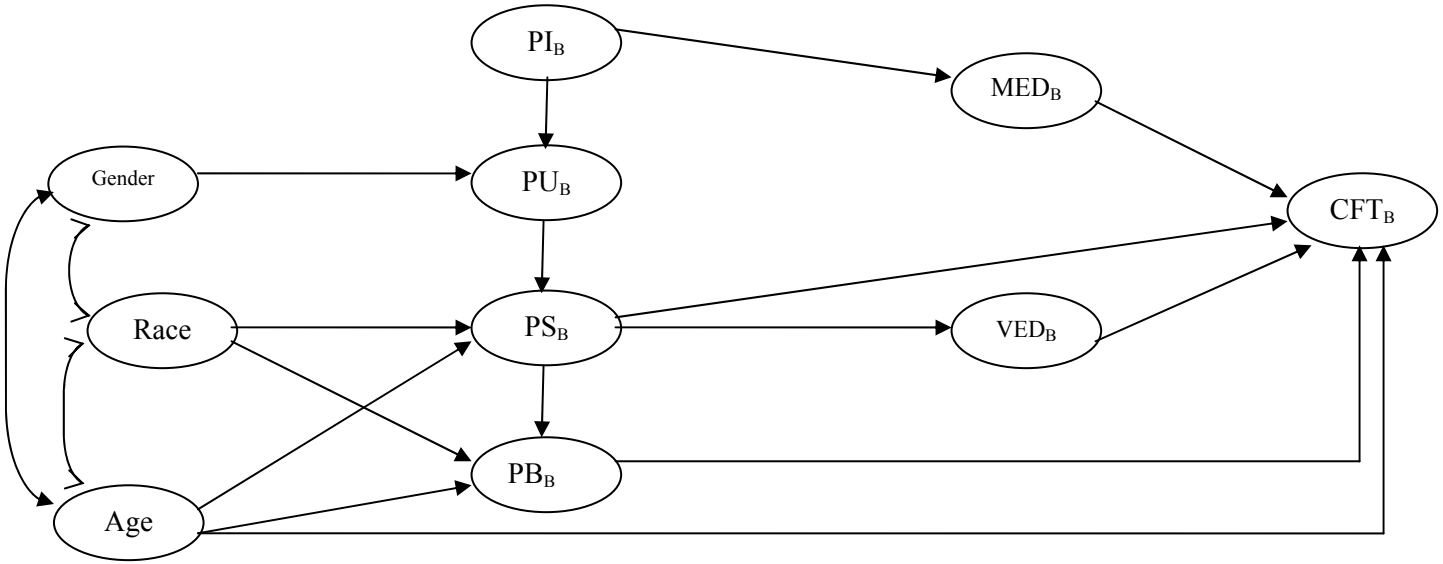
extensively established. The PASAT is capable of detecting very subtle impairments in information processing ability; thus, one of the most commonly used measure to assess attention. Performance on the PASAT in pain patients is impaired.[264,265 ,266] Performance on PASAT did not deteriorate with long-acting narcotic use.[267] Since, the PASAT is sensitive to the factors being studied; it will be included in this study.

In summary, we can conclude that pain experience is adequately described by the stages of pain model. Further, stage III and IV of the model are directly associated with cognitive processes, which may contribute to sub-normal performance in tasks that require concentration, memory, focus, and persistence. The review in chapter 1 demonstrated that opioid analgesics tend to have a minimal negative association with cognitive test scores, particularly in pain patients that derive analgesic benefit from the drug.

Given this background information, the following model is proposed to examine the associations between stages of pain model variables, narcotic analgesic dose, benzodiazepine dose and cognitive function as measured through neuropsychological test in CNMP patients. Figure 2.2 is a representation of all the relationships outlined above.

[264] Sletvold H, Stiles TC, Landro NI. Information processing in primary fibromyalgia, major depression, and healthy controls. *The Journal of Rheumatology*. 1995;22:137-142.
[265] Iezzi T, Archibald Y, Barnett P, Klinck A, Duckworth M. Neurocognitive performance and emotional status in chronic pain patients. *Journal of Behavioral Medicine*. 1999;22:205-216.
[266] Grace GM, Nielson WR, Hopkins M, Berg MA. Concentration and memory deficits in patients with fibromyalgia syndrome. *Journal of Clinical and Experimental Neuropsychology*. 1999;21:477-487.
[267] Sjogren P, Olsen AK, Thomsen AB, Dalberg J. Neuropsychological performance in cancer patients; the role of oral opioids, pain and performance status. *Pain.* 2000;86:237-245.

Figure 2.2 Structural Equation Model Depicting Associations between Demographics (age, gender, ethnicity), Stages of Pain Model Variables, Narcotic and Benzodiazepine Dose, and the Dependent Variable (cognitive function test score) at Baseline

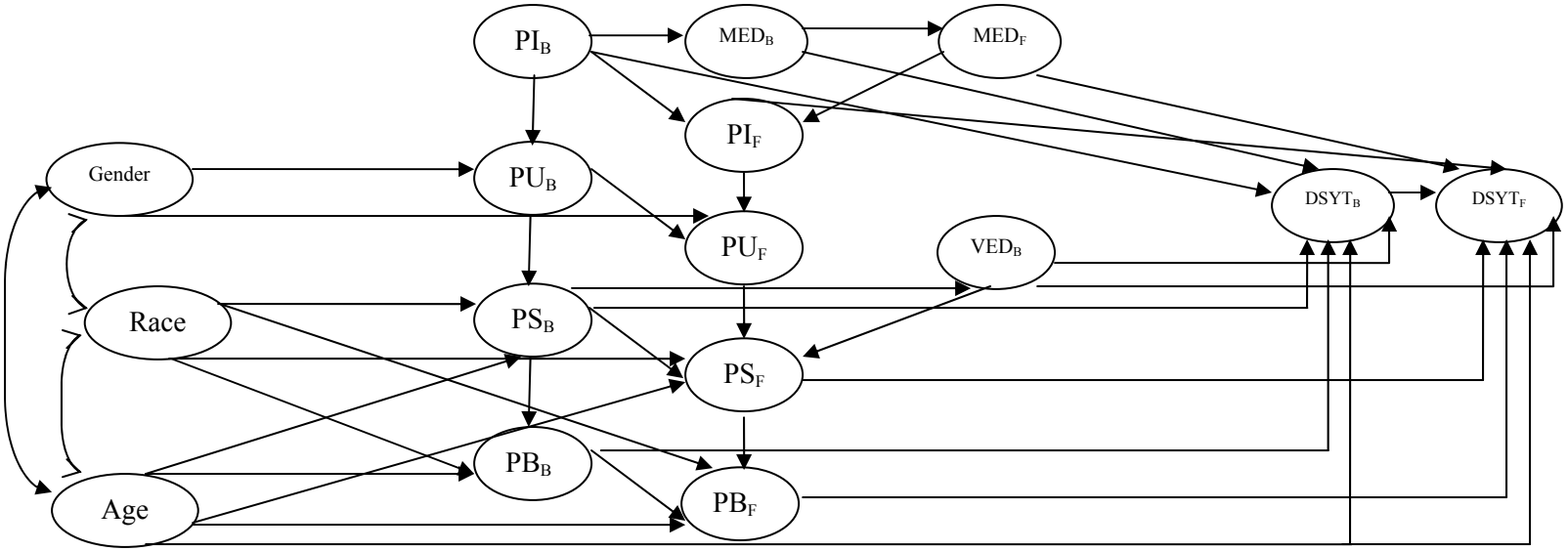


PI – Pain Intensity, PU – Pain Unpleasantness, PS – Pain Suffering, PB - Pain Behaviors, MED – Morphine Equivalent Dose, VED - Valium Equivalent Dose, CFT – Cognitive Function Test Score, B – Baseline, ↖↗ indicates that two variables covary

2.4 Hypothesized Study Model

Data for each variable (excluding demographics) in the proposed path model will be collected at baseline and follow-up. Data for patients on each variable collected at baseline and follow-up are expected to be correlated. Therefore, Figures 2.3, 2.4, and 2.5 represent two wave models with the digit span test, digit symbol test, and paced auditory serial addition test as dependent variables. Since each of these models will be analyzed separately, hypothesis for each model are presented after the representative figure.

Figure 2.3- Proposed Two-wave Path Diagram with Digit Span Test as the Dependent Variable



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, DSYT-Digit Span Test, B-Baseline, F-Follow-up

2.4 Hypothesis

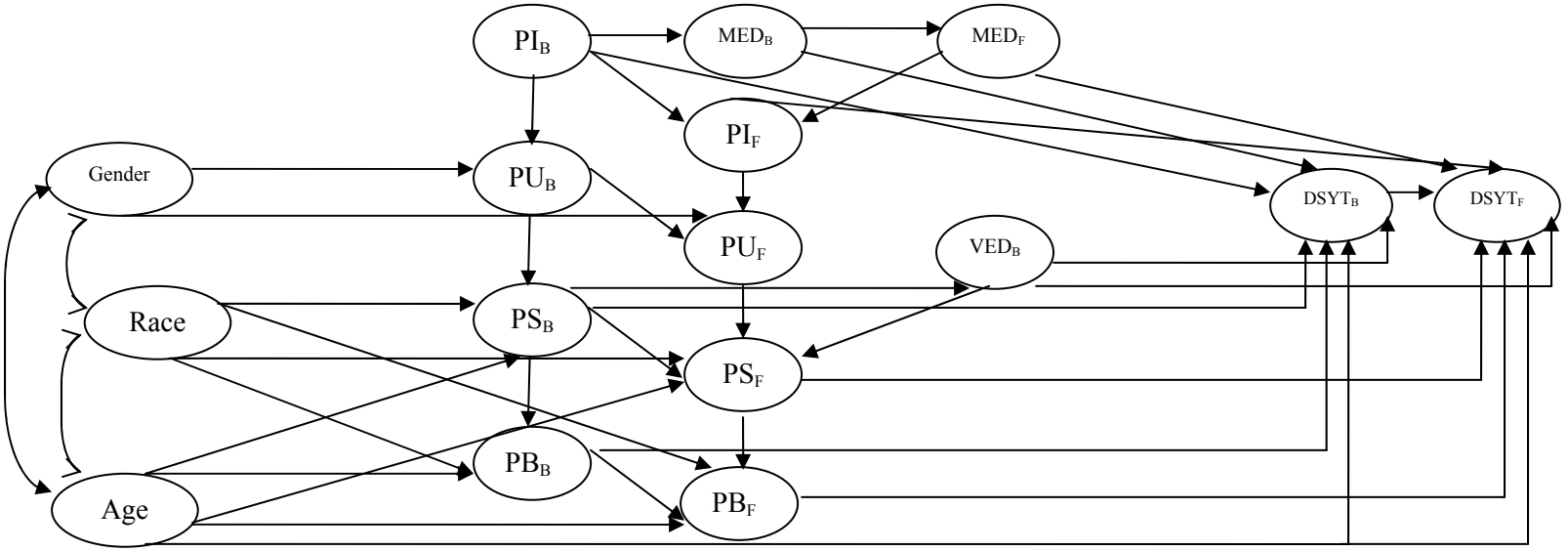
2.4.1 Hypothesis for Digit Span Model

The following hypothesis will be tested for the proposed two-wave path model (Figure 2.3) with the Digit span subtest as the dependent variable:

- H_{o1}: There is no significant association between morphine equivalent dose (MEU) of short-acting narcotic analgesic agents and digit span subtest scores at baseline.
- H_2: There is a significant linear and inverse relationship between benzodiazepine dose and digit span subtest scores baseline.
- H_{o3}: There is no significant direct association between pain intensity and digit span subtest scores at baseline.
- H_4: There is a significant linear and inverse association between pain suffering and digit span subtest scores at baseline.
- H_5: There is a significant linear and inverse association between frequency of pain behaviors and digit span subtest scores at baseline.
- H_6: There is a significant linear and inverse association between age and pain suffering at baseline.
- H_{o7}: There is no significant difference in pain unpleasantness ratings between males and females at baseline.
- H_{o8}: There is no significant association between ethnicity and pain suffering at baseline.
- H_{o9}: There is no significant association between ethnicity and pain behavior at baseline.
- H_{o10}: There is no significant association between age and pain behavior at baseline.
- H_{11}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.
- H_{12}: There is linear and direct association between pain suffering and valium equivalent dose at baseline

- H_{13}: There is an inverse association between age and DST at baseline.
- H_{o14}: There is no significant association between morphine equivalent dose (MEU) of long-acting narcotic analgesic agents and digit span subtest scores at follow-up.
- H_{15}: There is a significant linear and inverse relationship between benzodiazepine dose and digit span subtest scores at follow-up.
- H_{o16}: There is no significant direct association between pain intensity and digit span subtest scores at follow-up.
- H_{17}: There is a significant linear and inverse association between pain suffering and digit span subtest scores at follow-up.
- H_{18}: There is a significant linear and inverse association between frequency of pain behaviors and digit span subtest scores at follow-up.
- H_{19}: There is a significant linear and inverse association between age and pain suffering at follow-up.
- H_{o20}: There is no significant difference in pain unpleasantness ratings between males and females at follow-up.
- H_{o21}: There is no significant association between race and pain suffering at follow-up.
- H_{o22}: There is no significant association between race and pain behavior at follow-up.
- H_{o23}: There is no significant association between age and pain behavior at follow-up.
- H_{24}: There is an inverse association between morphine equivalent dose and pain intensity at follow-up.
- H_{25}: There is an inverse association between valium equivalent dose and pain suffering at follow-up.
- $H_{26:}$ There is an inverse association between age and DST at follow-up.

Figure 2.4- Proposed Two-wave Path Diagram with Digit Symbol Test as the Dependent Variable



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, DSYT-Digit Symbol Test, B-Baseline, F-Follow-up

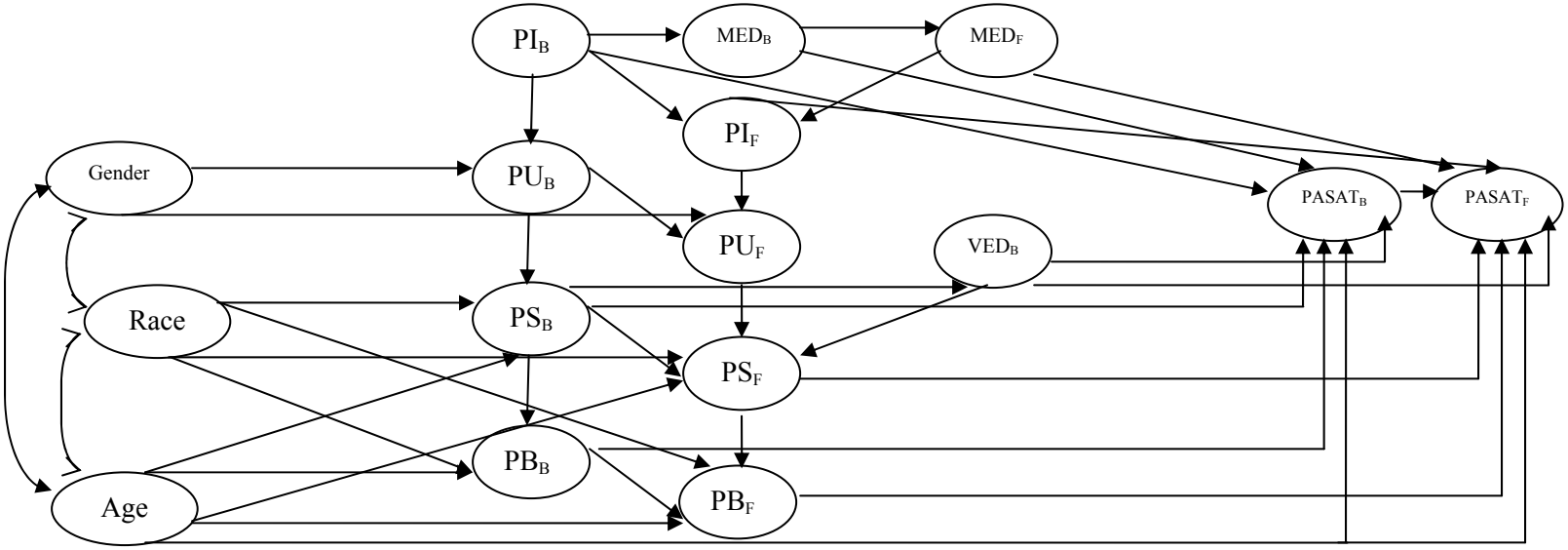
2.4.2 Hypothesis for Digit Symbol Model

The following hypothesis will be tested for the proposed two-wave path model (Figure 2.4) with the Digit symbol subtest as the dependent variable:

- H_{o27}: There is no significant association between morphine equivalent dose (MEU) of short-acting narcotic analgesic agents and digit symbol subtest scores at baseline.
- H_{28}: There is a significant linear and inverse relationship between benzodiazepine dose and digit symbol subtest scores baseline.
- H_{o29}: There is no significant direct association between pain intensity and digit symbol subtest scores at baseline.
- H_{30}: There is a significant linear and inverse association between pain suffering and digit symbol subtest scores at baseline.
- H_{31}: There is a significant linear and inverse association between frequency of pain behaviors and digit symbol subtest scores at baseline.
- H_{31}: There is a significant linear and inverse association between age and pain suffering at baseline.
- H_{o32}: There is no significant difference in pain unpleasantness ratings between males and females at baseline.
- H_{o33}: There is no significant association between ethnicity and pain suffering at baseline.
- H_{o34}: There is no significant association between ethnicity and pain behavior at baseline.
- H_{o35}: There is no significant association between age and pain behavior at baseline.
- H_{36}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.
- H_{37}: There is linear and direct association between pain suffering and valium equivalent dose at baseline
- H_{38}: There is an inverse association between age and DSYT at baseline.

- H_{o39}: There is no significant association between morphine equivalent dose (MEU) of long-acting narcotic analgesic agents and digit symbol subtest scores at follow-up.
- H_{40}: There is a significant linear and inverse relationship between benzodiazepine dose and digit symbol subtest scores at follow-up.
- H_{o41}: There is no significant direct association between pain intensity and digit symbol subtest scores at follow-up.
- H_{42}: There is a significant linear and inverse association between pain suffering and digit symbol subtest scores at follow-up.
- H_{43}: There is a significant linear and inverse association between frequency of pain behaviors and digit symbol subtest scores at follow-up.
- H_{44}: There is a significant linear and inverse association between age and pain suffering at follow-up.
- H_{o45}: There is no significant difference in pain unpleasantness ratings between males and females at follow-up.
- H_{o46}: There is no significant association between race and pain suffering at follow-up.
- H_{o47}: There is no significant association between race and pain behavior at follow-up.
- H_{o48}: There is no significant association between age and pain behavior at follow-up.
- H_{49}: There is an inverse association between morphine equivalent dose and pain intensity at follow-up.
- H_{50}: There is an inverse association between valium equivalent dose and pain suffering at follow-up.
- $H_{51:}$ There is an inverse association between age and DSYT at follow-up.

Figure 2.5- Proposed Two-wave Path Diagram with Paced Auditory Serial Addition Test as the Dependent Variable



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, PASAT-Paced Auditory Serial Addition Test, B-Baseline, F-Follow-up

2.4.3 Hypothesis for Paced Auditory Serial Addition Test Model

The following hypothesis will be tested for the proposed two-wave path model (Figure 2.5) with the paced auditory serial addition test (PASAT) as the dependent variable:

- H_{o52}: There is no significant association between morphine equivalent dose (MEU) of short-acting narcotic analgesic agents and PASAT scores at baseline.
- H_{53}: There is a significant linear and inverse relationship between benzodiazepine dose and PASAT scores baseline.
- H_{o54}: There is no significant direct association between pain intensity and PASAT scores at baseline.
- H_{55}: There is a significant linear and inverse association between pain suffering and PASAT scores at baseline.
- H_{56}: There is a significant linear and inverse association between frequency of pain behaviors and digit PASAT scores at baseline.
- H_{57}: There is a significant linear and inverse association between age and pain suffering at baseline.
- H_{o58}: There is no significant difference in pain unpleasantness ratings between males and females at baseline.
- H_{o59}: There is no significant association between ethnicity and pain suffering at baseline.
- H_{o60}: There is no significant association between ethnicity and pain behavior at baseline.
- H_{o61}: There is no significant association between age and pain behavior at baseline.
- H_{62}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.
- H_{63}: There is linear and direct association between pain suffering and valium equivalent dose at baseline
- H_{64}: There is an inverse association between age and PASAT at baseline.

- H_{o65}: There is no significant association between morphine equivalent dose (MEU) of long-acting narcotic analgesic agents and PASAT scores at follow-up.
- H_{66}: There is a significant linear and inverse relationship between benzodiazepine dose and PASAT scores at follow-up.
- H_{o67}: There is no significant direct association between pain intensity and PASAT scores at follow-up.
- H_{68}: There is a significant linear and inverse association between pain suffering and PASAT scores at follow-up.
- H_{69}: There is a significant linear and inverse association between frequency of pain behaviors and PASAT scores at follow-up.
- H_{70}: There is a significant linear and inverse association between age and pain suffering at follow-up.
- H_{o71}: There is no significant difference in pain unpleasantness ratings between males and females at follow-up.
- H_{o72}: There is no significant association between race and pain suffering at follow-up.
- H_{o73}: There is no significant association between race and pain behavior at follow-up.
- H_{o74}: There is no significant association between age and pain behavior at follow-up.
- H_{75}: There is an inverse association between morphine equivalent dose and pain intensity at follow-up.
- H_{76}: There is an inverse association between valium equivalent dose and pain suffering at follow-up.
- $H_{77:}$ There is an inverse association between age and PASAT at follow-up.

Chapter 3: Methodology

3.1 Study Design

This study utilizes a prospective design in which patients will be evaluated over a period of four weeks. A within subjects design will be employed with measures obtained at two points in time.

$$O_B \quad X \quad O_F$$

O_B – Observations at baseline

X – Therapeutic intervention (long-acting narcotic analgesics)

O_F – Observations at follow-up

Participants will include chronic non-malignant pain patients that have been referred to *Advanced Pain Management and Rehabilitation Medical Group Inc.*, Castro Valley, CA. A convenience sampling procedure shall be used for this pre-experimental design. Patients with moderate to severe chronic non-malignant pain who have received a previous trial of short-acting narcotic analgesics (SANA) (hydrocodone, codeine, propoxyphene, etc.) will be recruited for the study.

The physician has control of who will be changed from a short-acting narcotic analgesic to a long-acting narcotic analgesic. This responsibility is not in control of the researcher. The division of responsibilities between the clinician and researcher is detailed in Table 3.1. In order for patients to be initiated on long-acting narcotic therapy patients must be receiving treatment with short-acting narcotic analgesics and meet these additional criteria:

- Experience constant chronic pain despite adhering to SANA regimen;
- Inadequate pain relief, which requires frequent SANA dosing;
- Flares in pain symptoms;
- Risk of hepatic toxicity due to excessive consumption of acetaminophen along with SANA therapy;

- Disturbed sleep patterns;
- Lack of improvement in function with SANA.

Typically, patients encountered at the clinic present with these characteristics and these patients are routinely converted to long-acting narcotic analgesic therapy after evaluation by the clinician. In most cases, patients will be initiated on the lowest Avinza dose (30mg) and the physician will instruct patients to modify SANA dose as appropriate. The determination of appropriateness of long-acting therapy is made solely on the basis of clinical criteria, which will in no way be influenced by the need to enroll patients in the study. This decision is part of current practice in the clinic.

Once the clinician has determined the need for initiation of long-acting narcotic therapy and sought their interest to participate in the study, he will introduce the patient to the researcher. Figure 3.1 provides an illustration of the point at which the researcher will make contact with the patient. The researcher will provide patients who express an interest in the study with a study flyer (See Appendix B) and seek interest in participation. Patients will be enrolled in the study if they voluntarily agree to participate and complete an informed consent form (See Appendix C).

Once patients agree to volunteer in the study, a convenient time will be scheduled to obtain measures at baseline. The following assessments will be made at baseline: pain intensity, pain unpleasantness, pain suffering, pain behaviors, depression (Beck Depression Inventory -BDI), short-acting narcotic analgesic dose, benzodiazepine dose, and measures of attention. Additionally, background information (birth date, medical record number, medications, diagnosis, type of pain, duration of pain and prior surgery) indicated in Appendix D will be obtained from patient charts. Patients will be asked to report average daily dose of short-acting narcotic analgesic and benzodiazepine (if applicable) in the previous week. Retrieving this information within the last week should not pose a significant burden on patient memory. Additionally, using the average daily dose of SANA and benzodiazepines within the last week would be suitable for the purpose of the analysis. Unless otherwise noted,

this information will be obtained by self-report and verification will be obtained through prescription records when possible.

Following baseline assessments, patients will be evaluated after a two-week interval to assess pain relief, side effects, and need for breakthrough medication. Patients will have the ability to obtain appointments immediately in the event of an emergency. Pain intensity assessments made for the purposes of titrating dosage and monitoring progress will not be included in the path model. An example of the progress assessment guide can be found in Appendix G. Dose adjustments shall be made in the following situations:

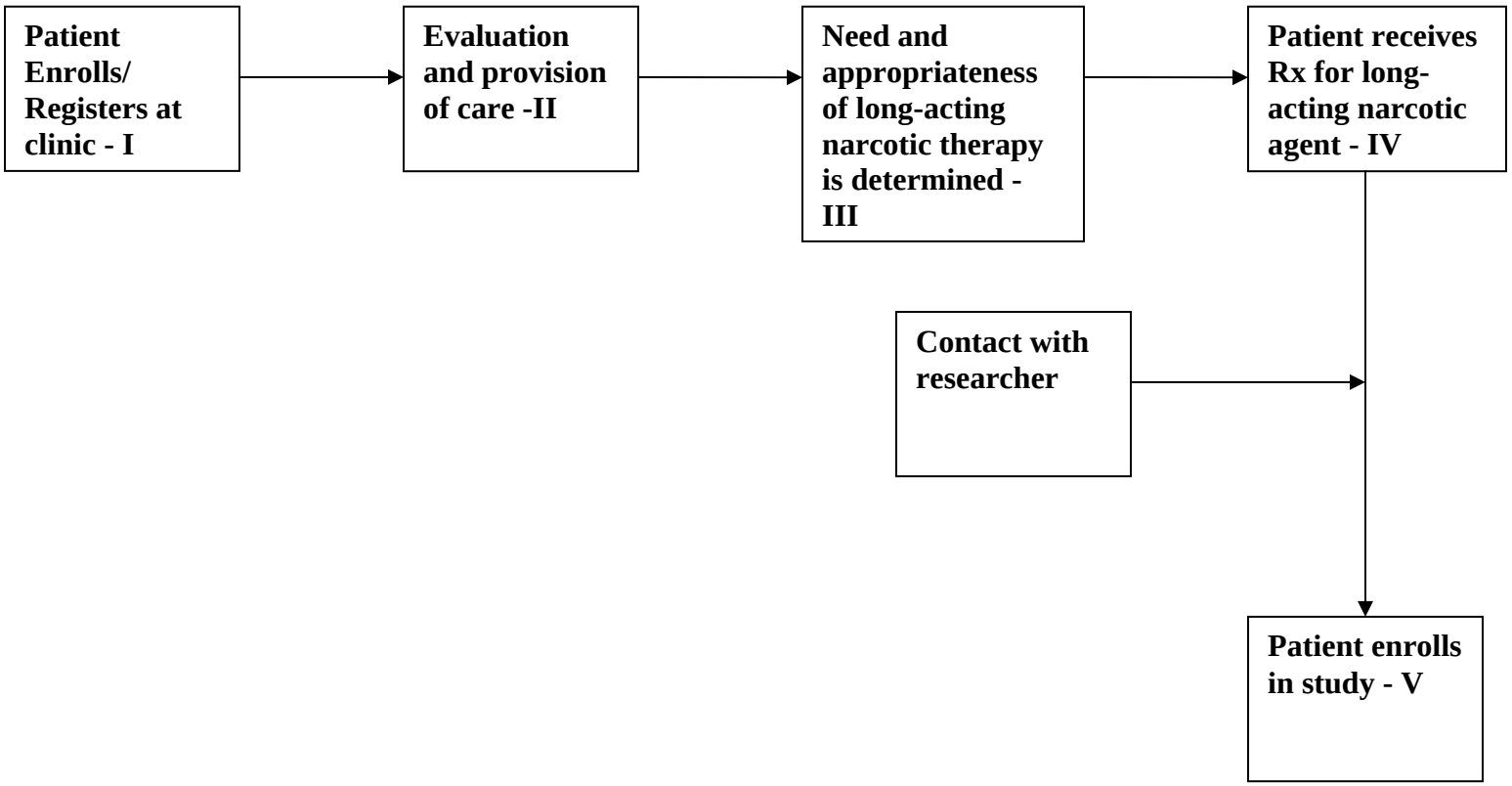
- Less than 50 percent improvement in pain relief as reported by the patient;
- Greater than four doses of breakthrough medication;
- Intolerable or unmanageable side-effects.

Data collection sheets used to obtain baseline data will also be used at follow-up. These follow-up measures will be incorporated in the two-wave path model. An illustration of the flow of patients through baseline and follow-up assessments is presented in Figure 3.2.

Patients who are intolerant to Avinza or drop-out of the study due to side-effects, or do not obtain adequate pain relief will be switched to another medication. Data for these patients will not be included in the two-wave model.

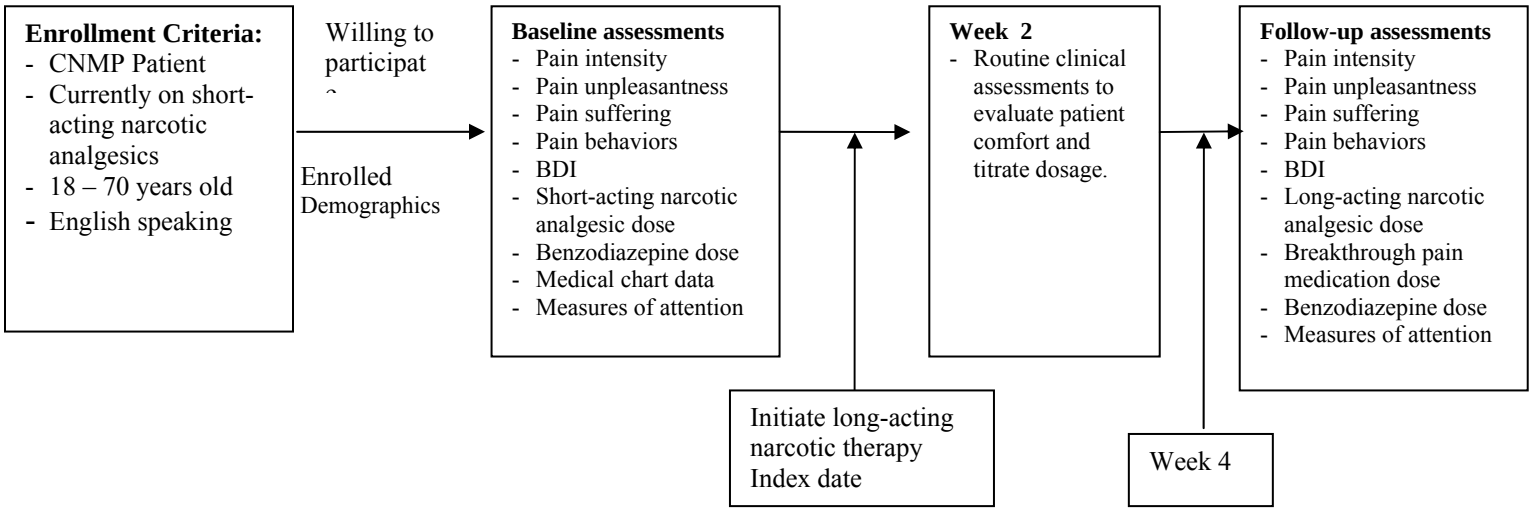
Table 3.1 - Division of Responsibilities between Physician/Clinic Staff and Researcher at Clinic Site	
Physician/Clinic Staff - Usual Responsibilities	*Researcher Responsibilities*
Pre-Visit ➢ *Visit Preparation* ▪ *Referring MD (Consult)* ▪ *Ancillary (X-rays)* ➢ *Referral/Prior Authorization* ➢ *Appointment Scheduled* ➢ *Benefit Eligibility* ➢ *Pre-registration* ➢ *Insurance Verification* ➢ *Medical record creation* ***Check-In*** ➢ *Registration* ➢ *Insurance verification* ➢ *Co-pay collection* ➢ *Clinical Intake* ***Provision of Care*** ➢ *Clinical care* ▪ *Assessments* ▪ *Diagnostics* ▪ *Treatment (Including long-acting narcotics)* ▪ *Ancillary Services* ▪ *Procedures* ➢ *Data collection* ➢ *Documentation of care* ➢ *Patient education* ➢ *Care coordination* ➢ *Coding* ➢ *Charge Capture* ➢ *Informs patient about study* ***Check-Out*** ➢ *Charge entry* ➢ *After hours care* ➢ *Follow-up care (Progress Assessment Guide)* ***Follow-up Care*** ➢ *Evaluation of therapy* ➢ *Treatment optimization*	***Pre-Visit*** ➢ *None* ***Check-In*** ➢ *None* ***Provision of Care*** ➢ *None* *If patient has been prescribed long-acting narcotic analgesic:* ➢ *Researcher contacts patient once patient has expressed interest to learn more about the study.* ➢ *Provide study flier* ➢ *Solicit interest in participation* ➢ *Schedule appointment* ***Assessments*** ➢ *Background Information* ➢ *Pain assessments* ➢ *Neuropsychological testing* ***Follow-up Assessments*** ➢ *Pain assessments* ➢ *Neuropsychological testing* ➢ *Follow-up assessment data obtained from progress assessment guide*

Figure 3.1 – Division of Responsibilities and Point of Contact between Patients and Researcher



Phases I to IV represent routine activities at the clinic site and are under complete control of the physician. Patient contact with researcher will occur only after the decision to prescribe long-acting narcotic analgesic has occurred. At this point, patient willingness to enroll in the study will be determined.

Figure 3.2 – Flow Chart of Study Protocol, Enrollment Criteria, Baseline and Follow-up Assessments



3.2 Sample Characteristics

In addition to chronic non-malignant pain (CNMP -defined as pain that has persisted for three or more months), patients must meet the following inclusion criteria: English speaking, 18-70 years of age, be under the care of physician (Ravi Panjabi, MD) at the clinic site mentioned above. These patients should also be receiving treatment with SANA and meet criteria for being initiated on long-acting narcotic therapy.

Patient exclusion criteria include: pain not responding to opioids, a history of allergy or hypersensitivity to opioids, life threatening disease, reduced level of consciousness, social isolation, history of substance misuse, clinically relevant cardiac, nervous system, or respiratory disease. The goal of the study is to recruit a total of 100 patients. In order to detect a moderate treatment effect (effect size = 0.15), the study with 100 participants shall have sufficient power (0.80) to draw inferences at the 95 percent confidence level.

3.2.1 Patient Recruitment

Eligible patients will be informed about the study by the physician-in-charge and will be requested to contact the researcher about study details if patients express an interest to participate in the study. Participants will be notified that the purpose of the study is to assess the effects of the medications that will be prescribed to treat their pain and their willingness to participate or decline in the study shall in no way interfere with the care they receive at the clinic. An appointment will be scheduled with patients that volunteer to participate in the study. Data will be collected at baseline and a follow-up assessment will be made at the end of four weeks.

3.2.2 Sample Size Calculations

The few studies that have addressed the relationship between cognitive function and long acting narcotic analgesics in chronic non-malignant pain have failed to address the issue of sample size. An adequate sample size is necessary to enable the researcher to reject the null hypothesis with a certain degree of confidence, and conclude that the phenomenon in question does exist. [268]

The following parameters are of concern with tests of statistical inference: power $(1 - \beta)$ i.e., power = 0.80 is considered substantial to detect treatment effect; α – significance level in most cases is estimated at the 0.05 level; effect size – the extent to which the phenomenon exists in the population, and N- sample size. Given any of these three parameters, the fourth can be determined. In estimating any of these parameters consideration must also be given to the statistical test employed.

The data will be analyzed using path analysis, which utilizes several multiple regression equations to test the relationships specified within the model. For the purposes of this study, two models have been specified. The follow-up model includes one additional predictor, i.e., route of administration of long-acting narcotic agent. Patients at follow-up will conceivably utilize short-acting agents for breakthrough pain. The total amount of drug used at follow-up will be calculated as the average daily dose of the long-acting and short acting narcotic analgesic in the precious week. Path analysis is discussed in greater detail below.

It is clear from the description above that in order to calculate sample size for the purposes of a study, effect size of the phenomenon under question must be estimated. There are several ways to arrive at this estimate, such as, reviewing the literature or utilizing conventional effect size estimates that have been proposed by Cohen:

1. Small Effect size: $R^2 = 0.0196$ (approximately 2 percent of the variance in the dependent variable)
2. Medium Effect size: $R^2 = 0.13$ (13 percent of the variance in the dependent variable)
3. Large Effect size: $R^2 = 0.25$ (25 percent of the variance in the dependent variable)

268 Cohen J. Statistical power for the behavioral sciences. Lawrence Erlbaum Associates Inc. New York, NY. 1982.

For the purposes of this study, an effect size estimate will be gauged from the literature. A summary of the studies with relevant effect size estimates is provided in Table 3.1 below. All of these studies examined the association between one or more independent variables, such as, pain intensity, depression, opioid dose, pain beliefs, pain behaviors and scores on cognitive tests among chronic non-malignant pain patients. Cohen has provided a formula to calculate sample size for a multiple regression analysis, which is depicted here:[269]

$$N = \lambda / f^2$$

$$N = \lambda (1 - R^2_{Y.B}) / R^2_{Y.B}$$

N- Sample size

λ – non centrality parameter of the non central F- distribution

$R^2_{Y.B}$ – proportion of variance accounted for by B (set of one or more independent variables) in dependent variable Y

$1 - R^2_{Y.B}$ - proportion of error or residual variance

λ is a simple function of the ES (effect size) index and the numerator and denominator df (degrees of freedom), respectively u and v:[270]

$\lambda = f^2 (u + v + 1)$

where,

$f^2 = R^2_{Y.B} / (1 - R^2_{Y.B})$

The value for λ can be calculated from tables provided by Cohen. This value can be estimated from the following parameters α, power, u (total number of independent variables), and v (denominator degrees of freedom). Specific values of λ can be determined for four values of v (20, 60, 120, and ∞). Linear interpolation will yield an accurate estimate of λ. However, using v = 120 yields values of λ that are sufficiently accurate. Use of the following parameter values: u = 15, α = 0.05, v = 120, power = 0.80 yielded a λ value of 19.0.

[269] Cohen J. Statistical power for the behavioral sciences. Lawrence Erlbaum Associates Inc. New York, NY. 1982.
[270] Ibid.

Substituting λ =17.4 and an effect size estimate of 0.15 in equation 1 yields a sample size of 98.

N = 19.0 (1 – 0.15) / 0.15

N = 107

A total of 130 patients shall be recruited utilizing a convenience sampling strategy and measures will be obtained at baseline and follow-up.

Table 3.2. Summary of Studies with Relevant Effect Size Estimates

STUDY/DESCRIPTION	CF TEST	R^2
Haythornwaite et al. assessed cognitive function in patients treated with either long acting (n = 19) and short acting (n = 10) narcotic analgesics.	DST DSYT	0.27 0.56
Francis examined the effect of long term administration of short-acting narcotic agents on cognitive function in chronic pain patients Change in test scores were regressed on change in pain intensity, BDI scores, and MEU from Time 1 to Time 2.	DSF DSB	0.27 NS
Sjogren and colleagues compared 40 age-matched healthy controls with 40 chronic non-malignant pain patients treated with long-acting narcotics for at least 2 weeks. SVAS, PVAS, HAD, Karnofsky performance status, opioid doses were measured. Only PVAS correlated with PASAT scores.	PASAT (T- 2.4 sec) PASAT (T- 2.0 sec)	0.18 0.36
Wade and colleagues examined the association between the stages of pain model and scores on the Digit span test (forward and backward test scores combined) in chronic non-malignant pain patients	DST	0.11

CF Test – Cognitive Function Test, BDI- Beck depression inventory, MEU – Morphine equivalent units, SVAS – Sedation visual analog scale, PVAS – pain visual analog scale, HAD – Hospital anxiety and depression scale, DST – Digit Span Test, DSYT – Digit Symbol Test, DSF – Digits Span Forwards, DSB – Digits Span Backwards, PASAT – Paced auditory serial addition test.

3.3 Instruments

The background information sheet and the scales to measure the 'stages of pain model' variables are listed in Appendix D. The items for the stages of pain model scales are the same as those used by Wade and colleagues in their confirmatory factor analysis of the model. The following scales will be administered to patients at baseline as well as follow-up:

3.3.1 Pain Intensity

Pain intensity represents the first stage of the stages of pain model, and is a measure of perceived pain intensity. Patients will be asked to report subjective pain at the highest intensity, lowest intensity, and usual intensity in the last week. Responses are indicated by marking along a visual analogue scale (VAS) that measures 15 cm in length with verbal anchors "no sensation" and "the most intense sensation imaginable." The VAS is presented in Appendix D. These three indicators will be used to load on the pain intensity construct, which represents stage I of the stages of pain model.

3.3.2 Pain Unpleasantness

Pain unpleasantness represents the second stage of the stages of pain model. Pain unpleasantness encompasses a patient's "immediate affective response to the pain sensation and to the context in which it occurs.[271]" Patients will be asked to report subjective pain unpleasantness due to pain at the highest intensity, lowest intensity, and usual intensity in the last week. Responses are indicated by marking along a VAS that measures 15 cm in length with verbal anchors "not bad at all" and "the most intense bad feeling possible." The VAS is presented in appendix D.

Price and colleagues have used the following statement to enable patients to distinguish between pain intensity and pain unpleasantness:

[271] Riley JL, Robinson ME, Wade JB, Myers CD, Price DD. Sex differences in negative emotional responses to chronic pain. *The Journal of Pain*. 2001;2:354-359.

> There are two aspects of pain which we are interested in measuring: the intensity, how strong the pain feels, and the unpleasantness, how unpleasant or disturbing the pain is for you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you.[272]
>
> These are scales for measuring each of these 2 aspects of pain. Although some pain sensations may be equally intense and unpleasant, we would like you to judge these 2 aspects of your pain independently.[273]

In a comparison of numerical rating scales and mechanical visual analogue scales it was concluded that only the latter fulfilled the properties of being ratio scales, while both scales were useful in distinguishing between pain intensity and unpleasantness, and experimental and clinical pain.[274]

3.3.3 Pain Suffering

The third stage of the stages of pain model is also referred to as pain suffering or pain affect. The construct is composed of two sub-factors, namely, negative emotions and negative beliefs. The following negative pain beliefs will be evaluated with the aid of visual analogue scales: pain interference, ability to endure pain, control over pain, and belief about curability. Item statements used to assess each belief item along with anchors for associated VASs can be viewed in Appendix D. Items used to assess pain beliefs had relatively low factor loadings (highest loading was 0.47) on the pain suffering construct. Wade and colleagues found that the fit obtained by the stages of pain

[272] Price DD, MCGrath PA, Rafii A, Buckinham B. The validation of visual analogue scales as ration scale measures for chronic and experimental pain. *Pain*. 1983;17:45-56.
[273] Harkins SW, Price DD, Braith J. Effects of extraversion and neuroticism on experimental pain, clinical pain, and illness behavior. *Pain.* 1989;36:209-218.
[274] Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain*. 1994,56:217-226.

model to the data without the negative belief variables was significantly better than with the variables included.[275]

The following negative emotions will be evaluated with the aid of visual analogue scales: depression, anxiety, frustration, anger, and fear. Patients indicate the level of each negative emotion they experience on a scale with anchor that range from "none" to "the most severe imaginable." The nine indicator variables will be loaded on the pain suffering construct.

3.3.4 Pain Behavior

Pain behaviors will be assessed from five subscales adapted from the psychological pain inventory (PPI). Items on the PPI are worded in an open ended format. Spontaneous responses reported by the patient are recorded followed by asking the patient about all the behaviors listed under each item. The authors argue that utilizing an open ended format in which patients are quizzed about each behavior elicits 'complete and reliable information.[276]' The following aspects of pain behaviors at home are recorded: patient actions in response to pain in the home, extent of "social reinforcement for illness behavior," effect on usual activities that need to be performed at home, pain response to rest and minimization of activity, and observed pain behavior will be assessed. Higher scores on an item indicate that a certain pain behavior is more apparent in the present case than in most cases of chronic pain. The PPI was originally designed to identify and assess problem areas that can be targeted for intervention.

The degree to which patients express pain behaviors at home is directly related to the extent of social reinforcement for pain behavior. It is believed that the extent to which pain patients relate with the sick role and the extent of reinforcement received are negatively correlated with desire to alter these behaviors. In addition to noting the type of behavior exhibited, accounting for the frequency of these behaviors enables distinguishing between patients.

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[275] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain.* 1996;68:157-167.
[276] Heaton RK, Gettto CJ, Lehman RAW, Fordyce WE, Brauer E, Groban SE. A standardized evaluation of psychosocial factors in chronic pain. Pain. 1982;12:165-174.

The item addressing the effect of pain on usual activities that need to be performed at home is a measure of direct change in activities that may have occurred subsequent to the pain problem. The number of daytime hours spent lying down or resting "is a direct measurement of the role that rest and avoidance of activity may have in the patient's pain.[277]" Patients that exhibit overt pain behaviors during the interview receive high scores. Additionally, patients who describe their pain as severe and persistent and do not exhibit behaviors that are concomitant with such a description receive high scores since the pain is exaggerated.

'Higher PPI scores predict increasing influence of psychosocial factors and poorer response to a treatment plan, while low scores are indicative of relatively fewer psychosocial factors that contribute to pain and influence outcome.'[278]

3.3.5 Beck Depression Inventory (BDI)

The BDI is a self-administered rating scale for the assessment of depression in psychiatric and non-psychiatric populations. Beck and colleagues originally developed the Beck Depression Inventory (BDI), in 1961.[279] The BDI is a 21-item instrument that has found wide application in the assessment of clinical depression.[280] The instrument is highly internally consistent with coefficients ranging from 0.73 to 0.92 in both psychitriac and non-psychiatric populations.[281]

The maximum score on each item is three, for a maximum score of sixty-three. The lowest possible score for the whole test is zero. For the current study, the item on suicidal ideation will not be included and hence maximum score that patients can obtain

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[277] Getto CJ, Heaton RK. Psychosocial pain inventory manual. Psychological Assessment Resources, Inc. Lutz, FL. 1995;pp:23.

[278] Heaton RK, Gettto CJ, Lehman RAW, Fordyce WE, Brauer E, Groban SE. A standardized evaluation of psychosocial factors in chronic pain. *Pain*. 1982;12:165-174.

[279] Beck AT, Ward CH, Mendelson M, Mock N, Erbaugh J. An inventory for measuring depression. *Archives of General Psychiatry*. 1961;4:561-571.

[280] Wade JB, Price DD, Hamer RM, Schwartz SM, Hart RP. An emotional component analysis of chronic pain. *Pain*. 1990;40:303-310.

[281] Beck AT, Steer RA, Garbin MG. Psychometric properties of the Beck Depression Inventory: Twenty-five years of evaluation. *Clinical Psychology Review*. 1988;8 (1), 77-100.

is 60. The instrument is listed in Appendix E and was selected to screening tool for depression since:

- The measures obtained on the pain suffering construct have been previously correlated with measures obtained on the BDI.
- The clinic site for the study currently employs the BDI for assessing depressive symptoms among their patients.

3.3.6 Benzodiazepine Equivalent Dose

In assessing the effects of long-acting narcotic agents on cognitive impairment in chronic pain, the ideal research design would exclude all patients on benzodiazepines. However, numerous chronic non-malignant pain patients in clinical practice are maintained on benzodiazepines. Eliminating these patients from the study would significantly limit the sample. Therefore, benzodiazepine dose is included in the model as a control variable. The effects of benzodiazepine on cognitive impairment will be controlled for statistically in the study model.

Data on type of benzodiazepine, frequency and strength of dose will be obtained from patients. Whenever possible, self-reported data will be verified using prescription records maintained in medical charts. The following conversion factors will be used to compare patients on the different benzodiazepines that they are currently taking:

Table 3.3 - Drug Dose Conversion Equivalent to 60mg Diazepam (Valium)[282]		
Benzodiazepine	**Dose (mg)**	**Diazepam(60mg) conversion factor**
Alprazolam(Xanax)	6	10.0
Chlordiazepoxide (Limbitrol)	150	0.4
Clonazepam (Klonipin)	24	2.5
Flurazepam (Dalmane)	90	0.6
Halazepam (Paxipam)	240	0.25
Lorazepam (Ativan)	12	5
Oxazepam (Serax)	60	1.0
Temazepam (Restoril)	60	1.0

NOTE: To find the dose of chlordiazepoxide equivalent to that of diazepam, multiply by 0.4. A dose of 150 mg of chlordiazepoxide is equivalent to a dose of 60 mg of diazepam. A dose of 100 mg is equivalent to a dose of 40 mg, etc.

3.3.7 Morphine Equivalent Dose

Patient reported information about the type(s), dose, and dose schedule of utilized narcotic medications will be obtained. Data will be verified using prescription records. Dose of short-acting narcotics will be converted to standardized morphine equivalent units. Equianalgesic dose conversion criteria listed in Table 1.3 will be used for the conversions.

3.3.8 Neuropsychological Tests

These tests will be administered to the patients at baseline and follow-up. The neuropsychological tests can be viewed in Appendix F.

The scales and tests will be administered in the following order. After providing each patient with a description of the study and obtaining their consent, patients will be asked to complete the scales assessing the stages of pain model variables. Following this, digit span and the digit-symbol tests well be administered in succession. Patients will then be asked whether they would prefer to complete the BDI or take a short break (2-3 minutes). After completing the BDI, patients will be provided another short break. Finally, the

[282] Miller NS, Gold MS. Management of withdrawal syndromes and relapse prevention in drug and alcohol dependence. *American Family Physician*. 1998;58:139-146.

PASAT, which takes about 15 minutes to complete will be administered. It is anticipated that the entire process will require approximately 45-50 minutes for completion.

3.3.8.1 Digit Span Test

The digit span subtest includes two tests, the digits forward and backward tests. For the digits forward test, patients are simply asked to repeat the series of numbers that was recited. A total of eight series, each with two trials are recited. One point is assigned for every series that is correctly recalled. Thus, a maximum of 16 points can be scored on the digits forward test. The total number of digits in each subsequent series increases from a minimum of two digits to a maximum of nine digits. The number of digits in each series refers to the span.

For the digits backward test, patients are asked to repeat the series of numbers that was recited in the reverse order. A total of seven series, each with two trials are recited. One point is assigned for every series that is correctly recalled. Thus, a maximum of 14 points can be scored on the digits backward test.

The raw score calculated represents the number of series correctly recalled. The raw scores can be converted into scaled scores based on age categories to draw comparisons with data from normal, healthy individuals and also draw comparisons within the sample. Although Lezac, recommends analyzing scores from the two tests separately, scaled norm scores are available for both tests combined. Studies have evaluated the validity and reliability of the test as an adequate measure of attention.[283,284,285] The test along with scoring manual and norms data is available from the Psychological Corporation, San Antonio, TX.

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[283] Larrabee GJ, Curtiss G. Construct validity of various verbal and visual memory tests. *Journal of Clinical and Experimental Neuropsychology.* 1995;17:536-547.

[284] Larrabee GJ, Kane RL, Schuck JR. Factor analysis of the WAIS and Wechsler Memory Scale: an analysis of the construct validity of the Wechsler Memory Scale. *Journal of Clinical Neuropsycholo*gy. 1983;5:159-168

[285] Snow WG, Tierney MC, Zorzitto ML, Fisher RH, Reid DW. WAIS-R test-retest reliability in a normal elderly sample. *Journal of Clinical and Experimental Neuropsychology* 1989;11:423-428.

3.3.8.2 Digit Symbol Test

The digit symbol test is a sub-test of the Wechsler Adult Intelligence Scale and assesses motor function and hand-eye coordination. A series of nine symbols corresponding to a number are printed on top of the record sheet. Also provided on the sheet is a total of 140 blank boxes along with a corresponding number. Subjects must fill each blank box with the symbol from the key provided at the top with the first seven boxes serving as a practice. Thus, a maximum raw score of 133 can be attained with the allotted two minutes for the task. The digit symbol test assesses various aspects of psychomotor function such as motor persistence, sustained attention, response speed, and visuomotor coordination. The digit symbol test was found to have little association ($r = 0.22$ to 0.44) with other subtests of intelligence that are part of the WAIS-R indicating that the test is independent of mental ability.

3.3.8.3 Paced Auditory Serial Addition Test

The paced auditory serial attention test is a measure of information processing, and sustained attention. Subjects are presented with single digit numbers in a random order. and they are required to add each number to the one immediately before it. Each subject undergoes four trials. Sixty digits are presented in a trial with the speed of digit presentation increasing with each subsequent trial (2.4, 2.0, 1.6, 1.2 seconds). On several occasions, subjects may experience difficulty with the two slower rates of presentation, in such a situation the two trials with 1.6 and 1.2 second digit presentation rates are not administered. Spreen and Strauss provide detailed oral administration instructions, for example:

"I am going to ask you to add together pairs of single-digit numbers, You will hear a tape-recorded list of numbers read one after the other, I will ask you to add the numbers in pairs and give your answers out loud. Although this is really a concentration task, and not a test to see how well you can add, it might help to do a little adding before I explain the task in detail. Please add the following pairs of numbers as fast as you can and give your answers out loud: 3,8(11); 4,9(13);7,8(15);…..7,6(13). Good.

The task that I want you to do involves adding together pairs of numbers, just like you have done, except that the numbers will be read as a list, one after the other, Let me give you an example with a short, easy list. Suppose I gave you the following: 1,2,3,4. Here is what you would do. After hearing the first two numbers on the list, which were 1,2, you would add these together and give your answer, 1+2 = 3. The next number on the list is 3, so when you heard it, you would add this number to the number right before it on the list which was 2, and give your answer, 2+3 = 5. Are you following so far? The last number you heard is 4 (remember the list is 1,2,3,4), so you would add 4 to the number right before it, which was 3, and give your answer, 3 + 4 = 7. The important thing to remember is that you must add each number on the list to the number right before it on the list, and not to the answer you have just given. You can forget your answers as soon as you have said them. All you have to remember is the last digit that you have heard and add it to the next digit that you hear. O.K? Let's try that short list again, only this time you say the answers. Ready? 1,2, (3), 3, (5), 4, (7). Now let's try another, longer practice list of numbers, This time the numbers on the list won't be in any particular order. Ready? 4,6, (10), 1, (7), 8, (9), 8, (16), 4, (12), 3, (7), 8, (11), 2, (10), 7, (9). Good.[286]"

In addition to oral instruction, written instructions are also available for patients that have difficulty in understanding the test procedure.Normative data obtained from healthy subjects are presented below: It is evident from the table that performance on the PASAT declines with increasing rate at which digits are presented.

Table 2.3 – Mean Number of Correct Responses at Each Age Range[287]

	Age in years					
Presentation rate (in seconds)	**16-29 (n = 30)**		**30-49 (n = 30)**		**50-69 (n = 30)**	
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
2.4	47.4	10.1	43.4	10.2	43.5	13.6
2.0	42.0	12.5	41.9	10.2	35.6	14.6
1.6	36.0	13.0	33.1	12.2	30.8	15.9
1.2	27.4	9.9	24.6	10.6	21.2	14.4

SD – Standard deviation

Source: Stuss et al. (1988) provide normative data from a sample of healthy relatively well-educated adults, ages 16-69 years.

[286] Spreen O, Strauss E. *A compendium of neuropsychological tests. Administration, norms, and commentary.* Oxford University Press. New York,NY. 1998; pp:244.
[287] Spreen O, Strauss E. *A compendium of neuropsychological tests. Administration, norms, and commentary.* Oxford University Press. New York,NY. 1998.

3.4 Data Analysis

The procedures used to analyze data obtained from the sample of patients are discussed below. SPSS version 11.0 and AMOS version 4.0 will be used for all the analyses. All tests of statistical inference will be made at the 0.05 alpha level. Data analysis will include the following:

1. Descriptive statistics – A description of the sample on all relevant variables will be included by generating frequency distribution, means, and standard deviations.
2. Normality – In order to test for normality, histograms and statistics for skewness and kurtosis will be generated. Appropriate transformations will be applied to variables that grossly violate the normality assumption.
3. Outlier variables will be excluded from the data.
4. Confirmatory factor analysis/Structural equation modeling will be used to validate the measures used in the stages of pain model.
5. Structural equation modeling will be used to test the hypothesized models.

Patients will be encouraged to fill all forms thoroughly during the interview data to minimize missing data. Data for patients who do not complete follow-up assessments will not be included in the two-wave models. Data will be screened to eliminate coding errors by running frequencies and descriptives for each variable. Skewness and kurtosis values for each variable will be examined to verify that data meet assumptions of normality.

3.4.1 Analyses Plan

The proposed study models will be analyzed with causal modeling techniques. More specifically, structural equation modeling (SEM), which is a combination of factor analysis and path analysis will be used to analyze collected data. SEM is also commonly referred to as covariance structure modeling.

In order to utilize causal modeling, there must be sufficient confidence in the theory being posited. Prior knowledge serves as a guide to make restrictive assumptions about the structure of the data. Consequently, the objective in SEM is to minimize the

difference between the observed covariance matrix and the restricted covariance matrix (i.e., the hypothesized model).

In order to determine whether the operationalized variables of the stages of pain model load on the constructs they are purported to measure, a hybrid model testing the measurement structure and the relations between latent constructs will be analyzed with baseline and follow-up data. Such an analysis will serve to confirm the measurement component and the structural component of the baseline and follow-up stages of pain models. The models may be modified to improve fit to the data. The evaluation of structural equation models are governed by numerous criteria. A description of some of these criteria and how they will be applied in the current study are discussed next.

3.4.2 Goodness of Fit Statistics

The most common test to evaluate model fit to the data is the exact chi-square fit test. The chi-square statistic tests the plausibility of a significant difference between the hypothesized model and a just-identified version of that model. A non-significant value of the chi-square statistic ($p > 0.05$) indicates that fit of the over-identified model does not differ from fit of the null model, and the hypothesized model is acceptable.[288]

Several fit indices have been developed to assist in evaluation of various aspects of model fit. The Joreskog-Sorbom goodness of fit index can be considered as a parallel to the squared multiple correlation. The index explains the proportion of the sample variance-covariance matrix accounted for by the hypothesized model. The normed fit index (NFI) is indicative of the percentage improvement in fit of the hypothesized model over the null model.

The standardized root mean square residual (SRMR) is most sensitive to misspecified factor structures while the comparative fit index (CFI), Bollen's fit index (BL89), and root mean square error of approximation (RMSEA) are sensitive to poorly specified factor loadings. In order to adequately assess factor loadings and latent

[288] Kline RB. Principles and practice of structural equation modeling. The Gulford Press. New York, NY. 1998.

structure of the current model the following goodness of fit indices will be evaluated: SRMR, CFI, RMSEA.[289]

Based on the fit indices, procedures such as removal of poorly loading items or measurement of parameters constrained to be zero may be employed. For the purpose of this analysis, operationalized variables with item loadings that are not significant ($p > 0.05$) will be eliminated.

Every model includes three types of variables, i.e., exogenous variables, endogenous variables, and disturbance terms, which account for error not accounted for by variables in the model. A system of linear equations is used to simultaneously examine the association between several exogenous and endogenous variables. These associations are modeled in the form of path diagrams, which enable a visual conceptualization of the postulated theory.[290] These techniques encompass path analysis and structural equation modeling. The path coefficients estimated are interpreted as regression coefficients in a multiple regression analysis. Maximum likelihood estimation procedures will be used to estimate path coefficients for the proposed model.

Causal modeling does not provide any information about the direction of the relationship between two variables (X & Y) or that one variable causes another except under the following restrictive conditions:

- X and Y should covary;
- The variables should exhibit some temporal order;
- Elimination of confounders (believed to precede X & Y) should not alter the relationship between X and Y.[291]

[289] Hu L, Bentler PM. Fit indices in covariance structure modeling: sensitivity to underparametrized model misspecification. *Psychological Methods*. 1998;3:424-453.
[290] Byrne B. Structural equation modeling with EQA and EQS/Windows. Basic concepts, applications, and programming. Sage Publications. Thousand Oaks, CA. 1994.
[291] Asher HB. Causal modeling, Sage University paper series on quantitative applications in the social sciences 07-003. Newberry Park, Sage Publications, 11, 1983.

3.4.3 Advantages of Causal Modeling and Path Analysis[292]:

There are numerous advantages of path analysis over multiple regression techniques. Some advantages of path analysis include:

- Ability to separate the direct effects from the indirect effects of one variable on another variable.
    - Comparisons between the magnitudes of the direct and indirect effects can be drawn.
- The correlation between any two variables can be split into simple and compound paths, which can be summated to provide the total correlation
    - A compound path can be calculated by multiplying the simple paths that form the compound path.
- A comparison between observed variance-covariance matrix and that estimated from simple and compound paths can be used to determine the adequacy of model fit, i.e., goodness of fit testing.
    - Paths that have been omitted in the original model and are assumed to be zero can be tested by re-estimating the model with the path in question.
- Ability to manipulate empirical data within a theoretical context.

[292] Pedhazur EJ. Causal Analysis, In Multiple regression in behavioral research. CBS College Publishing. New York, NY. 1982.

The equations listed in Table 3.4 represent direct paths in the two-wave model with digit span test as dependent variable (Figure 2.3). Similar equations for models in Figure 2.4 and 2.5 will be estimated from the data as well.

Model Equations
$PU_B = G + PI + D_{PU_B}$
$PU_F = G + PI_F + PU_B + D_{PU_F}$
$PS_B = A + E + PU_B + D_{PS_B}$
$PS_F = A + E + PU_F + VED + PS_B + D_{PS_F}$
$PB_B = A + E + PS_B + D_{PB_B}$
$PB_F = A + E + PS_F + PB_B + D_{PB_F}$
$VED = PS_B + D_{VED}$
$MED_B = PI_B + D_{MED_B}$
$MED_F = MED_B + D_{MED_F}$
$PI_F = PI_B + MED_F - MED_B + D_{PI_F}$
$DST_B = A + PS_B + PB_B + MED_B + VED + PI_B + D_{DST_B}$
$DST_F = PS_F + PB_F + MED_F + VED + PI_F + DST_B + D_{DST_F}$

A – Age, G – Gender, E – Ethnicity/Race, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, DST-Digit Span Test, B-Baseline, F-Follow-up, D - Disturbance term associated with the latent variable

Chapter 4: Results

This results chapter can be summarized broadly under five sections. Concerns about the integrity of the data are addressed in the first section. This is followed by an overview of the demographic characteristics of the sample included in the study. Descriptive statistics for key variables that were assessed during the data collection phase are presented in section three. The final two sections present the confirmatory factor analysis procedure used to determine the study models and test hypothesis that were postulated.

4.1 Data Screening

A total of 129 patients were enrolled in the study. Baseline and follow-up data were obtained on 88 of these patients. The collected data were entered into a computer file. Accuracy of data input and coding were verified by cross checking entries in the computer file with data collection sheets. Item frequencies, and minimum and maximum scores were examined to determine that values were in specified ranges. SPSS 12.0 statistical software was employed to conduct exploratory data analysis.

4.1.1 Missing Data

Patterns of missing data may either be random or systematic. Systematic missing data cannot be subjected to statistical corrections and pose greater problems than observations missing at random.[293]

Complete observations were obtained for all variables except the Paced auditory serial addition test administered at a presentation rate of 2.4 and 2.0 seconds (PASAT 2.4 and 2.0). A total of eight patients did not complete the

[293] Kline RB. Principles and practice of structural equation modeling. The Gulford Press. New York, NY. 1998.

PASAT. Of these, three were lost to follow-up and three experienced side-effects. An additional two patients who completed both baseline and follow-up data for all other variables excluding the PASAT were excluded from models evaluating the PASAT as the dependent variable. Since there patients were included in models assessing the DST and DSYT as dependent variables (referred to as DST and DSYT models), the sample size in every model with PASAT as dependent variable (referred to as PASAT model) evaluated at baseline and follow-up included two fewer patients.

4.1.2 Outliers

Data were explored for univariate outliers. Outliers and extreme values can significantly affect the distribution of the data. Boxplots and standardized z-scores were used to identify extreme values. Tabachnik and Fidell suggest that cases with z-scores of $\left|3\right|$ or greater should be excluded from the dataset.[294]

Results from the exploratory analyses of baseline data identified three individuals whose short-acting narcotic analgesic morphine equivalent dose (MED) and one individual whose Valium equivalent dose (VED) exceeded the z-score threshold of $\left|3\right|$. One additional case had a morphine equivalent dose z-score value at follow-up that exceeded the above threshold.

Out of 129 patients who were enrolled, 30 experienced side-effects and 11 were lost to follow-up (see Table 4.1). Eighty-eight patients completed baseline and follow-up evaluations. Four of the five patients with extreme values had completed both follow-ups. Their elimination resulted in a usable sample size of 84 patients. An additional two patients who had baseline and follow-up data failed to complete the PASAT. Thus, the sample size of patients in the PASAT model was 82. Models with the digit span test and the digit symbol test as dependent variables included data from 84 patients. PASAT models included data from 82 patients.

[294] Tabachnick BG, Fidel LS. Using Multivariate Statistics (pp: 67). HarperCollins. New York, NY. 1996.

Table 4.1 – All Reasons for Subject Loss and Sample Size of Patients in the DST[a], DSYT[b], and PASAT[c] Models		
	n	(%)
Patients enrolled in study (Total)	129	(100.0)
Dropouts due to side-effects	26	(20.2)
Dropouts due to side-effects & incomplete PASAT[a]	3	(2.3)
Dropouts due to side-effects & outlier Value	1	(0.8)
Patients lost to follow-up	8	(6.2)
Patients lost to follow-up & incomplete PASAT[a]	3	(2.3)
Patients who completed study (one-month follow-up)	88	(68.2)
Patients who completed study (Total)	88	(100.0)
Patients who completed study & outlier value	4	(4.5)
DST & DSYT model sample size	84	(95.5)
Patients who completed study (Total)	88	(100.0)
Patients who completed study & outlier value	4	(4.5)
Patients who completed study & incomplete PASAT	2	(2.3)
PASAT model sample size	82	(93.2)

[a] DST – Digit Span Test
[b] DSYT – Digit Symbol Test
[c] PASAT – Paced Auditory Serial Addition Test

4.1.3 Normality

The maximum likelihood procedure for making unbiased parameter estimates in structural equation modeling assumes multivariate normality. Univariate normality was assessed by means of histograms and skewness and kurtosis values. Several Monte Carlo simulations have concluded that absolute values greater than $|3|$ represent extremely high skew and values greater than $|8|$ represent extreme kurtosis.[295,296]

[295] Chou CO, Bentler PM . Estimates and tests in structural equation modeling. In Hoyle RH, Structural Equation Modeling (pp 37-55). Thousand Oaks, CA:Sage. 1995.
[296] West SG, Finch JF, Curran PJ. Structural equation models with non-normal variables: problems and remedies. Estimates and tests in structural equation modeling. In Hoyle RH, Structural Equation Modeling (pp 56-75). Thousand Oaks, CA:Sage. 1995

All the modeled variables except MED at baseline (MED_B) and follow-up (MED_F) met the above criteria. After excluding the outlier cases, skewness values for MED_B and MED_F were 3.27 and 3.97 respectively. The kurtosis values for morphine equivalent dose at baseline and follow-up were 11.08 and 18.63 respectively. Therefore, a log transformation was performed for MED_B and MED_F values. The skew (1.00, 0.46) and kurtosis (1.19,1.34) values for natural log transformations of MED_B and MED_F were well within the acceptable range.

Calculated variances for variables hypothesized to be part of the model are presented in Table 4.2. Bolded figures represent variances with large magnitudes. According to Kline, large differences ($\geq$10) in the magnitude of variances of modeled variables can lead to failure of the maximum likelihood iterative process.[297] Additionally, the small sample size in this study may contribute to the failure in the iterative process. In order to minimize the extent to which variances for variables being modeled differed and improve the possibility of model convergence, baseline and follow-up scores for the following variables were also transformed to their natural log values: VED, PASAT 2.0 and 2.4, and digit symbol tests.

[297] Kline RB. Principles and Practice of Structural Equation Modeling. 1998. The Guilford Press. New York, NY.

Table 4.2 Variance Estimates of Indicators Included in the Hypothesized Study Model for Data obtained from Evaluable Patients at Baseline and Follow-up

Construct	**Indicator**	**Variance**	
		Baseline	**Follow-up**
Pain Intensity (PI)	PI – Usual level	5.3	9.0
	PI – Highest level	2.9	8.2
	PI – Lowest level	10.8	8.2
Pain Unpleasantness (PU)	PU – Usual level	10.33	12.1
	PU – Highest level	4.5	10.2
	PU – Lowest level	19.6	12.6
Pain Suffering (PS) – Negative beliefs	Interference due to pain	6.5	9.9
	Ability to endure pain	9.5	13.6
	Ability to control pain	12.7	10.5
	Belief that pain will be cured	17.4	16.8
Pan Suffering (PS) – Negative emotions	Depression	20.4	18.5
	Anxiety	19.1	16.8
	Frustration	11.3	15.3
	Anger	25.6	20.9
	Fear	24.2	19.3
Pain Behaviors (PB)	Pain behavior at home	0.91	0.80
	Home and family related responsibilities	1.0	0.84
	Pain contingent down time	1.2	1.0
	Social reinforcement of PB	0.49	0.47
	PB during interview	1.1	1.3
MED[a]	Morphine equivalent dose	**3291.9**	**3375.3**
VED	Valium equivalent dose	**117.3**	**147.5**
DSYT	Digit symbol test score	**267.5**	**268.6**
PASAT[b]	PASAT 2.4 score	**84.4**	**83.2**
	PASAT 2.0 score	**88.9**	**81.4**
DST	Digits span test - forward Score	4.8	5.4
	Digits span test - backward Score	3.5	4.6

Numbers in bold indicate variances with large magnitudes that may hinder the maximum-likelihood iterative process

[a] MED baseline – Total short acting morphine equivalent dose at baseline Med Follow-up – Sum of Avinza dose and total short-acting narcotic analgesic dose used for breakthrough pain

[b] PASAT – Paced Auditory Serial Addition Test

4.2 Sample Description

A total of 129 patients were enrolled in this study. Eighty-eight (68.2%) patients completed the one-month follow-up. The proportions of patients who completed the study versus those who dropped out due to adverse events associated with Avinza® are provided in Table 4.3 below:

Table 4.3 – Number and Proportion of Patients who Completed the Study, Dropped Out, and Failed to Follow-up

	n	(%)
Patients enrolled in study (Total)	129	(100.0)
Patients who dropped out due to side-effects	30	(23.3)
Patients lost to follow-up	11	(8.5)
Patients who completed study (one-month follow-up)	88	(68.2)

As described in the data screening section, usable data were obtained from 124 patients at baseline, after excluding outliers. Complete data were obtained from 84 patients (i.e., patients who provided both baseline and follow-up data after excluding outliers). Patients who provided complete baseline and follow-up data (n = 84) were categorized as evaluable patients. Patients who dropped out of the study or were lost to follow-up (n = 40), after excluding outliers were categorized as non-evaluable patients.

4.2.1 Adverse Events

Table 4.4 presents the frequency of adverse events or reasons provided by patients who dropped out of the study. The most common reasons for dropping out of the study were drowsiness (n = 14), fatigue (n = 8), allergies to morphine (n = 6), itching (n = 6), nausea (n = 5), confusion (n =4), inadequate pain control (n = 2), shortness of breath (n = 2), and rashes (n =2). Several patients (n = 17) cited two adverse events or reasons for dropping out of the study. Ten patients

cited one adverse event or reason and three patients cited three adverse events or reasons for dropping out of the study.

Table 4.4 – Total Counts of Each Adverse Event or Reason Provided by Patients who Dropped Out of the Study (N =30)		
Adverse Event	n	(%)
Drowsiness	14	(26.4)
Fatigue	8	(15.1)
Allergic to Morphine	6	(11.3)
Itching	6	(11.3)
Nausea	5	(9.4)
Confusion	4	(7.5)
Inadequate Pain Control	2	(3.8)
Shortness of breath	2	(3.8)
Rash	2	(3.8)
Constipation	1	(1.9)
Headaches	1	(1.9)
Vomiting	1	(1.9)
Dizziness	1	(1.9)
Total	53	(100.0)

*Total does not equal 100 due to rounding error

4.2.2 Demographic Characteristics

Table 4.5 presents the distribution of enrolled, evaluable and non-evaluable patients by age, gender, ethnicity, and education level. The average age of patients enrolled in the study was 46 years. Results from a t-test ($t = -0.27$, $df = 122$, $p = 0.78$) showed that the mean age of evaluable patients (46.6 years) did not differ significantly from that of non-evaluable patients (47.0 years). Additional t-test results ($t = -0.48$, $df = 122$, $p = 0.62$) showed that there was no statistically significant difference between the average age of males (47.2 years) and females (46.4 years) enrolled in the study.

A greater number of females (n = 74) than males (n = 50) were enrolled in the

study. Results from a chi-square test (chi-square = 7.79, df = 1, p = 0.005) showed that the proportion of females who did not complete the study (n = 31, 77.5%) was significantly greater those who did (n = 43, 51.2%).

A majority of enrolled patients (n = 76, 63.1%) were Caucasian. The sample of enrolled patients also consisted of the following ethnic groups: African-American (n = 25, 20.2%), Hispanic/Latin American (n = 12, 9.7%), American Indian (n =2, 1.6%), Asian (n = 4, 3.2%), and other (n = 5, 4.0%). Results from a chi-square test (chi-square = 1.51, df = 5, p = 0.91) showed no statistically significant difference in the ethnic composition of evaluable and non-evaluable patients.

The distribution of the highest level of education achieved by patients enrolled in the study was as follows: less than high school (n = 7, 5.6%) high school graduate (n = 41, 33.1%), some trade school or some college (n = 48, 38.7%), trade school or college graduate (n = 20, 16.1%), some graduate school (n = 4, 3.2%), graduate school (n = 4, 3.2%). %). Results from a chi-square test (chi-square = 2.38, df = 5, p = 0.79) showed no statistically significant difference between the education level of patients in the evaluable and non-evaluable groups.

A comparison of evaluable and non-evaluable patients by demographic characteristics showed that significantly more females dropped out of the study as compared to males. The results showed no significant differences between the two groups with respect to age, ethnicity, and education level.

Table 4.5 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients by Demographic Characteristics: Age, Gender, Race/Ethnicity, and Education Level						
Variable	Enrolled Patients[a]		Evaluable Patients[b]		Non-Evaluable Patients[c]	
	n	%	n	%	n	%
Age (years)						
18 – 29	3	(2.4)	1	(1.2)	2	(1.2)
30 – 39	20	(16.1)	13	(15.5)	7	(15.5)
40 – 49	56	(45.2)	39	(46.4)	17	(46.4)
50 – 59	35	(28.2)	27	(32.1)	8	(32.1)
60 – 69	10	(8.1)	4	(4.8)	6	(4.8)
Total	124	(100.0)	84	(100.0)	40	(100.0)
Mean	46.7		46.6		47.0	
SD	9.1		8.6		10.2	
Range	19 - 68		19 - 65		27 - 68	
Gender						
Female	74	(59.7)	74	(48.8)	31	(77.5)
Male	50	(40.3)	50	(51.2)	9	(22.5)
Total	124	(100.0)	124	(100.0)	40	(100.0)
Race/Ethnicity						
Caucasian	76	(61.3)	53	(63.1)	23	(57.5)
African-American	25	(20.2)	16	(19.0)	9	(22.5)
Hispanic/Latin American	12	(9.7)	8	(9.5)	4	(10.0)
American Indian	2	(1.6)	1	(1.2)	1	(2.5)
Asian	4	(3.2)	2	(2.4)	2	(5.0)
Other	5	(4.0)	4	(4.8)	1	(2.5)
Total	124	(100.0)	84	(100.0)	40	(100.0)
Highest Level of Education						
Less then high school	7	(5.6)	6	(7.1)	1	(2.5)
High school graduate	41	(33.1)	27	(32.1)	14	(35.0)
Some trade school/college	48	(38.7)	30	(35.7)	18	(45.0)
Trade school/college graduate	20	(16.1)	15	(17.9)	5	(12.5)
Some graduate school	4	(3.2)	3	(3.6)	1	(2.5)
Graduate school	4	(3.2)	3	(3.6)	1	(2.5)
Total	124	(99.9*)	84	(100.0)	40	(100.0)

* Total does not equal 100 due to rounding error

[a] All patients enrolled in the study at baseline excluding outliers

[b] All patients who completed baseline and follow-up assessments excluding outliers

[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.2.3 Duration of Chronic Non-Malignant Pain

Table 4.6 presents results on the distribution of patients by duration of pain. During the interview, patients were asked to state the amount of time (months or years) they had experienced the pain that was being treated (Appendix D). The mean duration of pain was 5.35 years. A majority (n = 72, 58.1%) of the enrolled patients had experienced pain for a duration of one to five years. A total of 38 patients (30.6%) had experienced pain for more than five years, and only 14 patients (11.3%) had experienced pain for less than one year. Results from a t-test (t = 0.62, df = 122, p = 0.53) showed no statisitical difference in the mean duration of pain between evaluable and non-evaluable patients.

Table 4.6 - Distribution of Sample by Duration of Pain for Enrolled, Evaluable, and Non-Evaluable Patients

Duration of Pain (years)	Enrolled Patients[a]		Evaluable Patients[b]		Non-Evaluable Patients[c]	
	n	%	n	%	n	%
Less than one	14	(11.3)	7	(8.3)	7	(17.5)
≥ One and ≤ Five	72	(58.1)	50	(59.5)	22	(55.0)
> Five	38	(30.6)	27	(32.1)	11	(27.5)
Total	124	(100.0)	84	(99.9*)	40	(100.0)
Mean	5.3		5.5		4.9	
SD	5.4		5.7		4.9	
Range	0.25 - 25		0.25 - 25		0.25 - 20	

* Total does not equal 100 due to rounding error
[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.2.4 Payment Source

Table 4.7 presents the distribution of results for enrolled, evaluable, and non-evaluable patients by payment source. Data on payment source were obtained through information recorded in patient charts. A total of 42.7 percent (n = 53)

of enrolled patients received medical and prescription benefits through worker's compensation. Other payment sources included HMOs (n = 17, 13.7%), PPOs (n = 22, 17.7%), Medicare (n = 6, 4.8%), MediCal (n = 8, 6.5%), Medicare and MediCal (n =12, 9.7%). Results from a chi-square comparison (chi-square = 5.15, df = 7, p = 0.6) showed that the two groups did not differ statistically by payment source.

Table 4.7 - Distribution of Sample by Payment Source for Enrolled, Evaluable, and Non-Evaluable Patients

Payment Source	Enrolled Patients[a]		Evaluable Patients[b]		Non-Evaluable Patients[c]	
	n	%	n	%	n	%
Worker's Compensation	53	(42.7)	33	(39.3)	20	(50.0)
HMO	17	(13.7)	12	(14.3)	5	(12.5)
PPO	22	(17.7)	17	(20.2)	5	(12.5)
Medicare	6	(4.8)	4	(4.8)	2	(5.0)
MediCal	8	(6.5)	5	(6.0)	3	(7.5)
Medicare/MediCal	12	(9.7)	9	(10.7)	3	(7.5)
Cash	3	(2.4)	1	(1.2)	2	(5.0)
Indemnity	3	(2.4)	3	(3.6)	0	(0.0)
Total	124	(100.0)	84	(100.1*)	40	(100.0)

* Total does not equal 100 due to rounding error
[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.2.5 Diagnoses

The data in Table 4.8 show that patients with a variety of diagnoses were included in the study. The total count of the top five most frequently occurring diagnoses among evaluable patients was as follows: lumbar spondylosis (51, 16.6%), lumbar disc disorder (47, 15.3%), radiculopathy (36, 11.7%), cervical spondylosis (27, 8.8%), and back pain (19, 6.2%). The total count of the top five

most frequently occurring diagnoses among non-evaluable patients was as follows: lumbar spondylosis (23, 17.4%), lumbar disc disorder (21, 15.9%), radiculopathy (18, 13.6%), cervical Spondylosis (10, 7.6%), and back pain (9, 6.8%).

The average number of diagnoses per individual was 3.6 and 3.3 in the evaluable and non-evaluable groups respectively. An eyeball comparison suggested that the rate at which the top five diagnoses occurred in the evaluable and non-evaluable groups were similar.

Table 4.8 Total Count of Each Diagnosis for which Evaluable (N = 84) and Non-Evaluable (N = 40) Patients were Treated at the Study Site				
Diagnoses	Evaluable[a]		Non-Evaluable[b]	
	n	(%)	n	(%)
Lumbar Spondylosis	51	(16.6)	23	(17.4)
Lumbar Disc Disorder	47	(15.3)	21	(15.9)
Radiculopathy	36	(11.7)	18	(13.6)
Cervical Spondylosis	27	(8.8)	10	(7.6)
Back Pain	19	(6.2)	9	(6.8)
Cervical Radiculopathy	15	(4.9)	5	(3.8)
Disc Disorder Cervical Region	15	(4.9)	4	(3.0)
Spinal Lumbar Degenerative Disc Disorder	10	(3.2)	1	(0.8)
Post Lumbar Laminectomy Syndrome	9	(2.9)	4	(3.0)
Disc Disorder Thoracic Region	7	(2.3)	1	(0.8)
Spinal Stenosis	7	(2.3)	4	(3.0)
Reflex Sympathetic Dystrophy Syndrome	6	(1.9)	3	(2.3)
(RSD)	5	(1.6)	1	(0.8)
Chronic Low Back Pain	5	(1.6)	3	(2.3)
Neck Pain	4	(1.3)	4	(3.0)
Cervical Pain	4	(1.3)	0	(0.0)
Foot Pain	4	(1.3)	3	(2.3)
Shoulder Pain	2	(0.6)	1	(0.8)
Chest Wall Pain	2	(0.6)	0	(0.0)
Fibromyalgia	2	(0.6)	2	(1.5)
Herniated Disc Lumbar	2	(0.6)	2	(1.5)
Hip Degenerative Joint Disease (DJD)	2	(0.6)	2	(1.5)
Hip Pain	2	(0.6)	2	(1.5)
Lumbar Sacral Spondylosis	2	(0.6)	0	(0.0)
Osteoarthritis	2	(0.6)	0	(0.0)
Post Laminectomy Syndrome Cervical Region	2	(0.6)	0	(0.0)
Thoracic Spondylosis	2	(0.6)	2	(1.5)
Wrist/Carpal Tunnel Syndrome	1	(0.3)	0	(0.0)
Extremity Pain	1	(0.3)	0	(0.0)
Hemarthrosis - Ankle	1	(0.3)	0	(0.0)
Intravertebral Herniation	1	(0.3)	0	(0.0)
Lumbar Compression Fracture	1	(0.3)	0	(0.0)
Lumbar Vertebral Syndrome	1	(0.3)	0	(0.0)
Migraine Headache	1	(0.3)	0	(0.0)
Osteomyelitis	1	(0.3)	0	(0.0)
Plantar Fascitis	1	(0.3)	0	(0.0)
Rheumatoid Arthritis	1	(0.3)	0	(0.0)

Total number of diagnosis exceeds 124 as each patient may have multiple diagnoses.
[a]All patients who completed baseline and follow-up assessments excluding outliers
[b]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Table 4.8 (Continued) Total Count of Each Diagnosis for which Evaluable (N = 84) and Non-Evaluable(N = 40) Patients were Treated at the Study Site		
Diagnoses	Evaluable[a] n (%)	Non-Evaluable[b] n (%)
Sacroiliac Pain	1 (0.3)	1 (0.8)
Sciatica Pain	1 (0.3)	0 (0.0)
Shoulder Strain	1 (0.3)	0 (0.0)
Spinal Lumbar Fracture	1 (0.3)	0 (0.0)
Spinal Thoracic Degenerative Disease	1 (0.3)	0 (0.0)
Spondylopathy Unspecified	1 (0.3)	1 (0.8)
Thoracic Pain	1 (0.3)	0 (0.0)
Vertebral Compression Fracture	0 (0.0)	1 (0.8)
Abdominal Pain	0 (0.0)	1 (0.8)
Deep Vein Thrombosis	0 (0.0)	1 (0.8)
Edema	0 (0.0)	1 (0.8)
Trigeminal Neuralgia	0 (0.0)	1 (0.8)
Total	308 (100.0)	132 (100.0)

Total number of diagnosis exceeds 124 as each patient may have multiple diagnoses.
[a]All patients who completed baseline and follow-up assessments excluding outliers
[b]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.3 Results of Key Model Variables

This section of the results chapter provides descriptive statistics for the key variables examined in the structural equation models. A brief description explaining the measurement technique for the variable will also be included.

4.3.1 Morphine Equivalent Dose (MED)

Patients enrolled in the study used a variety of short-acting narcotic analgesic medications. The dose of the narcotic medication used by enrolled patients was converted to a standard morphine milligram equivalent unit, which was labeled as morphine equivalent dose for the purposes of this study. The conversion criteria applied to convert the short-acting narcotic analgesic doses to standard morphine equivalent units can be viewed in Table 1.1 (page 26).

During the interview at baseline, patients were asked to provide the names and doses of prescription narcotic analgesic medications that they used to obtain pain relief. Patients were asked to recall the average number of narcotic analgesic doses taken per day in the previous week to obtain pain relief. The average daily short-acting narcotic analgesic dose used by the patient was calculated by multiplying the strength of the medications used with the number of doses. This average daily short-acting narcotic analgesic dose was converted to a morphine equivalent dose.

A similar procedure was utilized at follow-up. The average daily morphine equivalent dose at follow-up for each patient was calculated by adding the average daily Avinza® dose and the average daily short-acting narcotic dose used for breakthrough pain. Dose calculation for Avinza®, which is a long-acting morphine agent, did not require conversion to morphine equivalent units. The average daily dose of short-acting breakthrough pain medication at follow-up was calculated in a similar fashion to the short-acting narcotic analgesic morphine equivalent dose at baseline. Thus, the total narcotic analgesic dose at

follow-up was calculated as the sum of the Avinza® dose and the morphine equivalent dose (MED) of breakthrough pain medication at follow-up.

Table 4.9 presents the distribution of patients by brand name of primary short-acting narcotic analgesic used at baseline. A majority of enrolled patients (67.0%, n = 83) used various combinations of the short acting narcotic hydrocodone in combination with acetaminophen [Vicodin® (n = 27), Vicodin ES® (n = 26), Norco® (n = 22), and Lortab® (n = 8)]. Other short-acting narcotic analgesics commonly used by enrolled patients included methadone (10.5%, n = 13), Ultram® (7.2%, n = 9), Darvocet® (5.6%, n = 7). and Tylenol #4® (2.4%, n = 3). Tylenol #3®, morphine sulfate immediate release (MSIR), Actiq®, and Oxycodone® were used by two patients each.

Three categories of primary short-acting narcotic analgesic brands were created to assess differences in their use between evaluable and non-evaluable patients. One category of brands included all drugs in which the active ingredients were hydrocodone and acetaminophen. The second category of brands included drugs with methadone as the active ingredient, while the third category was an amalgam of brands with all other active ingredients. Results from a chi-square test (chi-square = 9.38 df = 2, p = 0.01) showed that there was a significant difference among primary narcotic analgesics used by evaluable and non-evaluable patients. The proportion of evaluable patients (72.6%) who utilized medications with hydrocodone/acetaminophen as active ingredients was higher than non-evaluable patients (55.0%). As compared to evaluable patients (4.8%), the proportion of patients in the non-evaluable group (22.5%) who used methadone was greater. The proportion of patients who utilized "other" brand names in each of the groups was similar (22.6% and 22.5%).

Table 4.9 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients by Brand of Primary Short-Acting Narcotic Analgesic Used to Treat Pain at Baseline

Narcotic Analgesic Brand Name	Enrolled Patients[c]		Evaluable Patients[d]		Non-Evaluable Patients[e]	
	n	(%)	n	(%)	n	(%)
Tylenol® #3	2	(1.6)	2	(2.4)	0	(0.0)
Tylenol® #4	3	(2.4)	3	(3.6)	0	(0.0)
Vicodin® 5/500	27	(21.8)	20	(23.8)	7	(17.5)
Vicodin ES®,[a] 7.5/750mg	26	(21.0)	20	(23.8)	6	(15.0)
Norco® 10/325mg	22	(17.7)	15	(17.9)	7	(17.5)
Lortab® 10/500mg	8	(6.5)	6	(7.1)	2	(5.0)
Ultram® 50mg	9	(7.2)	5	(6.0)	4	(10.0)
Methadone 10mg	13	(10.5)	4	(4.8)	9	(22.5)
MSIR[b] 15mg	2	(1.6)	1	(1.2)	1	(2.5)
Actiq® 200ug	2	(1.6)	2	(2.4)	0	(0.0)
Percodan 5mg	1	(0.8)	0	(0.0)	1	(2.5)
Oxycodone® 5mg	2	(1.6)	2	(2.4)	0	(0.0)
Darvocet® /Propoxyphene 100mg	7	(5.6)	4	(4.8)	3	(7.5)
Total	124	(99.9*)	84	(100.2*)	40	(100.0)

* Total does not equal 100 due to rounding error
[a]ES – Extra Srength
[b]MSIR – Morphine Sulfate Immediate Release
[c]All patients enrolled in the study at baseline excluding outliers
[d]All patients who completed baseline and follow-up assessments excluding outliers
[e]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Table 4.10 presents the distribution of enrolled, evaluable, and non-evaluable patients who used a second short-acting narcotic analgesic at baseline. A total of 12 patients (9.6%) used a second narcotic analgesic medication at enrollment. Among enrolled patients, five patients used Norco, two patients used Ultram, and one patient each used Vicodin, Vicodin ES, MSIR, Percocet, and Darvocet as a secondary narcotic analgesic. A similar proportion of patients in the evaluable (92.0%) and non-evaluable groups (87.5%) did not utilize a secondary narcotic analgesic.

Table 4.10 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients by Brand of Secondary Short-Acting Narcotic Analgesic Used to Treat Pain at Baseline

Narcotic Analgesic Brand Name	Enrolled Patients[c]		Evaluable Patients[d]		Non-Evaluable Patients[e]	
	n	(%)	n	(%)	n	(%)
Vicodin® 5/500	1	(0.8)	0	(0.0)	1	(2.5)
Vicodin ES®,[a] 7.5/750mg	1	(0.8)	0	(0.0)	1	(2.5)
Norco® 10/325mg	5	(4.0)	3	(3.6)	2	(5.0)
Ultram® 50mg	2	(1.6)	1	(1.1)	1	(2.5)
MSIR[b] 15mg	1	(0.8)	1	(1.1)	0	(0.0)
Percocet®	1	(0.8)	1	(1.1)	0	(0.0)
Darvocet® /Propoxyphene 100mg	1	(0.8)	1	(1.1)	0	(0.0)
Patients not on 2nd analgesic	112	(90.3)	77	(91.7)	35	(87.5)
Total	124	(100.0)	84	(100.0)	40	(100.0)

[a]ES – Extra Strength
[b]MSIR – Morphine Sulfate Immediate Release
[c]All patients enrolled in the study at baseline excluding outliers
[d]All patients who completed baseline and follow-up assessments excluding outliers
[e]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Table 4.11 presents the distribution of enrolled, evaluable, and non-evaluable patients by average daily morphine equivalent dose of short-acting narcotic analgesic at baseline. The categories were formed to correspond with the most commonly available Avinza dosage units (30mg, 60mg, 90mg and 120mg). A total of 40.3 percent (n = 50) of enrolled patients took an average daily MED that was less than or equal to 30 morphine milligram equivalents at baseline. Another 33.9 percent (n = 42) of enrolled patients used an average daily MED of short-acting narcotics that ranged from 30.1 to 60 morphine milligram equivalents. A total of 18 enrolled patients (14.5%) used an average daily MED that ranged from 60.1 to 120 morphine milligram equivalents. A total of 14 patients (11.3%) used an average daily MED that was greater than 120 morphine milligram equivalents. The number of non-evaluable patients (n = 9, 22.5%) who utilized a MED of short-acting narcotic analgesic at baseline that was greater than 180 mg was twice the number of evaluable

patients (n = 4, 4.8%). The average daily morphine equivalent short-acting narcotic analgesic dose utilized by enrolled patients at baseline was 76.56mg.

Results from an independent samples t-test (t = -3.64, df = 122, p < 0 .01) showed that the average daily MED taken by evaluable patients (mean MED = 52.3, sd = 57.3) was significantly lower than the average daily MED of short-acting narcotic analgesics taken by non-evaluable patients (mean MED = 128.9, sd = 175.1) at baseline.

Table 4.11 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients by Average Daily Morphine Equivalent Dose (MED) of Short-Acting Narcotic Analgesic at Baseline

MED (mg)	Enrolled Patients[a] n (%)	Evaluable Patients[b] n (%)	Non-Evaluable Patients[c] n (%)
0 to 30	50 (40.3)	38 (45.2)	12 (30.0)
30.1 to 60	42 (33.9)	32 (38.1)	10 (25.0)
60.1 to 90	13 (10.5)	7 (8.3)	6 (15.0)
90.1 to 120	5 (4.0)	2 (2.4)	3 (7.5)
120.1 to 180	1 (0.8)	1 (1.2)	0 (0.0)
> 180	13 (10.5)	4 (4.8)	9 (22.5)
Total	124 (100.0)	84 (100.0)	40 (100.0)
Mean	76.5	52.3	128.9
SD	115.1	57.3	175.1
Range	5 to 675	10 to 400	5 to 675

[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Table 4.12 presents the distribution of evaluable patients by average daily MED at follow-up. The table provides the distributions for average daily Avinza dose, MED of short acting narcotic breakthrough pain medication, and MED of total narcotic analgesic, which was calculated as the sum of Avinza and breakthrough pain medication doses.

A total of 37 patients (44.1%) used an average daily Avinza dose that was less than or equal to 30mg, while 68 patients (81%) used an average daily breakthrough pain medication dose that was less than or equal to 30mg units of morphine. Only 5 patients used a total narcotic dose that was less than or equal to 30mg units of morphine at follow-up.

A total of 33 patients (39.3%) utilized an average daily Avinza dose that ranged between 30.1mg and 60mg. A total of 11 (13.1%) patients utilized an average daily Avinza dose that was greater than 60 mg and less than or equal to 120 mg. Three patients (3.6%) utilized an average daily Avinza dose that was in excess of 120mg. The average daily Avinza dose utilized by patients at follow-up was 59.1mg (sd = 48.0).

A total of 12 patients (14.3%) utilized an average daily morphine equivalent breakthrough pain medication dose that ranged between 30.1mg and 60mg. Four patients (4.8%) utilized an average daily morphine equivalent breakthrough pain medication dose that exceeded 60mg. The average daily morphine equivalent breakthrough pain medication dose utilized by patients at follow-up was 23.6mg (sd = 32.4).

A total of 39.3 percent (n = 33) , 27.4 percent (n = 23), and 15.5 percent (n = 13) of patients utilized a total daily morphine equivalent narcotic dose at follow-up that ranged from 30.1mg to 60mg, 60.1mg to 90mg, and 90.1mg to 120mg, respectively. Ten patients (10.8%) of patients utilized a total daily morphine equivalent narcotic dose at follow-up that exceeded 120mg. The average total daily morphine equivalent narcotic dose utilized by patients at follow-up was 82.7mg (sd = 58.0).

Results form a paired sample t-test ($t = -6.6$, $df = 83$, $p < 0.01$) showed that the average daily morphine equivalent total narcotic dose (mean = 82.7, sd = 58.0) utilized by evaluable patients at follow-up was significantly greater than the average daily morphine equivalent short-acting narcotic dose at baseline (mean = 52.3, sd = 57.3).

Table 4.12 Distribution of Evaluable Patients by Average Daily Morphine Equivalent Dose (MED) of Avinza, Short-Acting Breakthrough Narcotic Analgesic, and Total Narcotic Analgesic at Follow-up

MED (mg)	Avinza n (%)	Breakthrough Narcotic Analgesic n (%)	Total Narcotic Analgesic[a] n (%)
0 to 30	37 (44.1)	68 (81.0)	5 (6.0)
30.1 to 60	33 (39.3)	12 (14.3)	33 (39.3)
60.1 to 90	7 (8.3)	2 (2.4)	23 (27.4)
90.1 to 120	4 (4.8)	0 (0.0)	13 (15.5)
120.1 to 180	1 (1.2)	1 (1.2)	6 (7.2)
> 180	2 (2.4)	1 (1.2)	4 (3.6)
Total	84 (100.1*)	84 (100.1*)	84 (100.0)
Mean	59.1	23.6†	82.7†
SD	48.0	32.4	58.0
Range	15 to 360	0 to 225	15 to 420

* Total exceeds 100 due to rounding error

[a] Total Narcotic Analgesic = (Avinza + Breakthrough Narcotic Analgesic)

† $p < 0.05$

4.3.2 Valium Equivalent Dose (VED)

Patients enrolled in the study used a variety of benzodiazepine medications. The dose of the benzodiazepine medication used by enrolled patients was converted to a standard Valium milligram equivalent unit, which was labeled as valium equivalent dose (VED) for the purposes of this study. The conversion criteria applied to convert the benzodiazepine medication doses to standard valium equivalent units can be viewed in Table 3.3 (page 47).

At baseline, patients were asked during the interview to provide the names and doses of prescription benzodiazepine medications that were used. Patients were asked to recall the average number of benzodiazepine doses taken per day in the previous week. The average daily benzodiazepine dose used by the patient was calculated by multiplying the strength of the medications used by the number of daily doses. This average daily benzodiazepine dose was converted to VED. Information provided by the patients was verified through prescription records maintained in the medical charts.

A similar procedure was utilized at follow-up. Patients reported no changes in benzodiazepine medication use at follow-up. Thus, the VED utilized by evaluable patients at baseline and follow-up was a constant.

Table 4.13 presents the distribution of enrolled, evaluable, and non-evaluable patients by brand name of benzodiazepine medication utilized at baseline. A similar proportion of enrolled (64.5%), evaluable (65.5%), and non-evaluable (62.5%) patients did not utilize benzodiazepines. Valium was the most frequently utilized benzodiazepine among enrolled (n = 18, 14.5%), evaluable (n = 11, 13.1%) and non-evaluable (n = 7, 17.5%)patients.

The distribution of enrolled patients across other commonly utilized benzodiazepines was as follows: Xanax® (n = 7, 5.6%), Ativan® (n = 7, 5.6%), Klonipin® (n = 6, 4.8%), Restoril® (n = 3, 2.4%), and Serax® (n = 3, 2.4%). The distribution of evaluable patients across commonly utilized benzodiazepines other

than Valium was as follows: Xanax® (n = 5, 6.0%), Ativan® (n = 3, 3.6%), Klonipin® (n = 4, 4.8%), Restoril® (n = 3, 3.6%), and Serax® (n = 3, 3.6%).

The distribution of non-evaluable patients across commonly utilized benzodiazepines other than Valium was as follows: Xanax (n = 2, 5.0%), Ativan (n = 4, 10.0%), and Klonipin, (n = 2, 5.0%).

Results from a chi-square test (chi-square = 0.10, df = 1, p = 0.74) showed no statistically significant difference between the proportion of evaluable and non-evaluable patients who used benzodiazepine medications.

Table 4.13 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients by Brand of Benzodiazepine Medication at Baseline

Benzodiazepine Medication Brand Name	Enrolled Patients[a]		Evaluable Patients[b]		Non-Evaluable Patients[c]	
	n	(%)	n	(%)	n	(%)
Valium®	18	(14.5)	11	(13.1)	7	(17.5)
Xanax®	7	(5.6)	5	(6.0)	2	(5.0)
Ativan®	7	(5.6)	3	(3.6)	4	(10.0)
Klonipin®	6	(4.8)	4	(4.8)	2	(5.0)
Restoril®	3	(2.4)	3	(3.6)	0	(0.0)
Serax®	3	(2.4)	3	(3.6)	0	(0.0)
Did not use Benzodiazepines	80	(64.5)	55	(65.5)	25	(62.5)
Total	124	(100.3)	84	(100.2)	40	(100.0)

[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Information on duration of benzodiazepine medication use was also obtained from patients who took the drugs listed in Table 4.13. Patients recalled from memory the duration of benzodiazepine use in terms of months or years. Table 4.14 presents the distribution of enrolled, evaluable, and non-evaluable patients who took benzodiazepines by duration of use. Duration of use categories were developed on the basis of relatively short-term use (≤ one year), long-term use (> one and ≤ five years), and persistent use that was greater than five years.

A total of 44 enrolled patients utilized benzodiazepines. Within this group, a total of 40.9 percent (n = 18) patients utilized benzodiazepines for less than or equal to one year. Another 38.6 percent (n = 17) utilized benzodiazepines for greater than one and less than or equal to five years, and 20.5 percent (n = 9) utilized these medications for greater than five years. The average benzodiazepine duration of use was 3.8 years.

A total of 29 evaluable patients utilized benzodiazepines. Within this group, a total of 48.3 percent (n = 14) patients utilized benzodiazepines for less than or equal to one year. Another 31.0 percent (n = 9) utilized benzodiazepines for greater than one and less than or equal to five years, and 20.7 percent (n = 6) utilized these medications for greater than five years.

A total of 15 non-evaluable patients utilized benzodiazepines. Within this group, a total of 26.7 percent (n = 4) patients utilized benzodiazepines for less than or equal to one year. Another 53.3 percent (n = 8) utilized benzodiazepines for greater than one and less than or equal to five years, and 20.0 percent (n = 3) utilized these medications for greater than five years.

Results from an independent samples t-test ($t = -0.14$, $df = 42$, $p = 0.88$) showed no statistically significant difference in the mean duration of benzodiazepine use between evaluable (3.8 years) and non-evaluable (4.0 years) patients.

Table 4.14 Distribution of Enrolled, Evaluable, and Non-Evaluable Patients who Use Benzodiazepine Medications by Duration of Use			
Benzodiazepine Medication Duration of Use (years)	Enrolled Patients[a] n (%)	Evaluable Patients[b] n (%)	Non-Evaluable Patients[c] n (%)
≤ one	18 (40.9)	14 (48.3)	4 (26.7)
> one and ≤ five	17 (38.6)	9 (31.0)	8 (53.3)
> five	9 (20.5)	6 (20.7)	3 (20.0)
Total	44 (100.0)	29 (100.0)	15 (100.0)
Mean	3.8	3.8	4.0
SD	5.3	5.9	4.1
Range	0.08 to 25	0.08 to 25	0.5 to 15

[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

Table 4.15 presents the distribution of enrolled, evaluable, and non-evaluable benzodiazepine users by VED. The average daily VED taken by enrolled patients who used benzodiazepine was 16.5mg. Among enrolled patients who used benzodiazepines, 47.7 percent (n = 21) utilized a daily VED that ranged from 2.5mg to 10mg. Another 27.3 percent (n = 12) of enrolled patients utilized a daily VED that was greater than 10mg and less than or equal to 20mg. Finally, 25.0 percent (n = 11) of enrolled benzodiazepine users utilized a daily VED that exceeded 20mg.

Among evaluable patients who used benzodiazepines, 48.3 percent (n = 14) utilized a daily VED that ranged from 2.5mg to 10mg. Another 27.6 percent (n = 8) of evaluable patients utilized a daily VED that was greater than 10mg and less than or equal to 20mg. Finally, 24.1 percent (n = 7) of evaluable benzodiazepine users utilized a daily VED that exceeded 20mg.

Among non-evaluable patients who used benzodiazepines, 46.6 percent (n = 7) utilized a daily VED that ranged from 2.5mg to 10mg. Another 26.7 percent (n = 4) of non-evaluable patients utilized a daily VED that was greater than 10mg and less than or equal to 20mg. Finally, 26.7 percent (n = 4) of non-evaluable benzodiazepine users utilized a daily VED that exceeded 20mg.

Results from a t-test (t = -0.19, df = 42, p = 0.85) showed that there was no statistically significant difference in the average daily valium equivalent dose between evaluable (mean = 16.8 mg, sd = 10.8) and non-evaluable patients (mean = 16.1, sd = 10.3).

Table 4.15 Distribution of Enrolled, Evaluable, and Non-Evaluable Benzodiazepine Users by Valium Equivalent Dose at Baseline

Valium Equivalent Dose (mg)	Enrolled Patients[a] n (%)	Evaluable Patients[b] n (%)	Non-Evaluable Patients[a] n (%)
≤ ten	21 (47.7)	14 (48.3)	7 (46.6)
> ten and ≤ twenty	12 (27.3)	8 (27.6)	4 (26.7)
> twenty	11 (25.0)	7 (24.1)	4 (26.7)
Total	44 (100.0)	29 (100.0)	15 (100.0)
Mean	16.5	16.8	16.1
SD	10.5	10.8	10.3
Range	2.5 to 40.0	2.5 to 40.0	2.5 to 30.0

[a] All patients enrolled in the study at baseline excluding outliers
[b] All patients who completed baseline and follow-up assessments excluding outliers
[c] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.3.3 Pain Intensity (PI)

Pain intensity was defined as "Stage I" of the stages of pain model. During the interview at baseline and follow-up, patients were asked to indicate the pain intensity experienced in the previous week at three levels: highest, lowest, and usual. In order to assess pain intensity at each of the three levels, patients were presented with three visual analogue scales that measured 15 centimeters (cm) in length. Each scale was anchored at the two ends by the following statements: "no sensation" and "the most intense sensation imaginable."

Table 4.16 presents the mean pain intensity ratings and corresponding standard deviations at highest, lowest, and usual levels for enrolled, evaluable, and non-evaluable patients. The mean pain ratings at the highest intensity level provided by enrolled (mean = 12.7 cm, sd = 1.7), evaluable (mean = 12.7 cm, sd = 1.7), and non-evaluable patients (mean = 12.6 cm, sd = 1.8) at baseline were

similar. Results from an independent sampless t-test ($t = 0.04$, $df = 122$, $p = 0.96$) showed that mean pain intensity ratings for highest pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 6.99$, $df = 83$, $p < 0.01$) showed that the mean pain intensity rating provided by evaluable patients for highest pain intensity level at follow-up (mean = 10.9, sd = 2.8) was significantly lower (mean difference = 1.8 cm, sd = 2.3) than at baseline, one month after treatment with Avinza®.

The mean pain ratings at the lowest intensity level provided by enrolled (mean = 6.7 cm, sd = 3.0), evaluable (mean = 6.7 cm, sd = 3.3), and non-evaluable patients (mean = 6.8 cm, sd = 2.5) at baseline were similar. Results from an independent samples t-test ($t = -0.14$, $df = 122$, $p = 0.88$) showed that mean pain intensity ratings for lowest pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 6.41$, $df = 83$, $p < 0.01$) showed that the mean pain intensity rating provided by evaluable patients for lowest pain intensity level at follow-up (mean = 4.5, sd = 2.8) was significantly lower than at baseline (mean difference = 2.2 cm, sd = 3.1), one month after treatment with Avinza®.

The mean pain ratings at the usual intensity level provided by enrolled (mean = 9.9 cm, sd = 2.4), evaluable (mean = 10.0 cm, sd = 2.3), and non-evaluable patients (mean = 9.9 cm, sd = 2.8) at baseline were similar. Results from an independent samples t-test ($t = 0.18$, $df = 122$, $p = 0.85$) showed that mean pain intensity ratings for usual pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 8.19$, $df = 83$, $p < 0.01$) showed that mean pain intensity rating provided by evaluable patients for usual pain intensity level at follow-up (mean = 7.6 cm, sd = 3.0) was significantly lower than at baseline (mean difference = 2.3 cm, sd = 2.6), one month after treatment with Avinza®.

Internal consistency reliability of the items used to form the pain intensity construct at baseline (Cronbach's $\alpha = 0.79$) and follow-up (Cronbach's $\alpha = 0.83$) was adequate.

Table 4.16 Means and Standard Deviations for Items Assessing Highest, Lowest, and Usual Pain Intensity Levels for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Pain Intensity VAS[g] – 15 cm	Enrolled Patients[d] n = 124 Baseline Scores	Evaluable Patients[e] n = 84 Baseline Scores	Non-Evaluable Patients[f] n = 40 Baseline Scores	Evaluable Patients[e] n = 84 Follow-up Scores
Highest Pain Intensity[a]				
Mean	12.7	12.7*	12.6	10.9*
SD	1.7	1.7	1.8	2.8
Lowest Pain Intensity[b]				
Mean	6.7	6.7*	6.8	4.5*
SD	3.0	3.3	2.5	2.8
Usual Pain Intensity[c]				
Mean	9.9	10.0*	9.9	7.6*
SD	2.4	2.3	2.8	3.0

[a] Indicate along the scale below the intensity of the painful sensation at its **highest intensity** during the past week.
[b] Indicate along the scale below the intensity of the painful sensation at its **lowest intensity** during the past week.
[c] Indicate along the scale below the intensity of the painful sensation at its **usual intensity** during the past week.
[d] All patients enrolled in the study at baseline excluding outliers
[e] All patients who completed baseline and follow-up assessments excluding outliers
[f] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
[g] VAS – 15cm – Visual Analogue Scale, length 15 centimeters
VAS Anchors: 0 cm – No Sensation, 15cm – The most intense sensation imaginable
* $p < 0.01$

4.3.4 Pain Unpleasantness (PU)

Pain Unpleasantness was defined as "Stage II" of the stages of pain model. During the interview at baseline and follow-up, patients were asked to indicate the pain unpleasantness experienced in the previous week at the highest, lowest, and usual pain intensity levels. In order to assess pain unpleasantness at each of the three levels, patients were presented with three visual analogue scales that

measured 15 centimeters (cm) in length. Each scale was anchored at the two ends by the following statements: "not bad at all" and "the most intense bad feeling possible."

Table 4.17 presents the mean pain unpleasantness ratings and corresponding standard deviations at highest, lowest, and usual levels for enrolled, evaluable, and non-evaluable patients.

The mean pain unpleasantness ratings at the highest pain intensity level provided by enrolled (mean = 12.9 cm, sd = 1.9), evaluable (mean = 12.8 cm, sd = 2.1), and non-evaluable patients (mean = 13.3 cm, sd = 1.5) at baseline were similar. Results from an independent samples t-test ($t = -1.39$, $df = 122$, $p = 0.16$) showed that the mean pain unpleasantness ratings at highest pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 5.74$, $df = 83$, $p < 0.01$) showed that mean pain unpleasantness rating provided by evaluable patients for highest pain intensity level at follow-up (mean = 11.0, sd = 3.2) was significantly lower (mean difference = 1.7 cm, sd = 2.7) than the mean unpleasantness rating for highest pain intensity level at baseline.

The mean pain unpleasantness ratings at the lowest pain intensity level provided by enrolled (mean = 6.8 cm, sd = 4.2), evaluable (mean = 6.5 cm, sd = 4.4), and non-evaluable patients (mean = 7.4 cm, sd = 3.8) at baseline were similar. Results from an independent samples t-test ($t = -1.15$, $df = 122$, $p = 0.25$) showed that the mean pain unpleasantness ratings at lowest pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 5.08$, $df = 83$, $p < 0.01$) showed that mean pain unpleasantness rating provided by evaluable patients for lowest pain intensity level at follow-up (mean = 4.0, sd = 3.5) was significantly lower (mean difference = 2.4 cm, sd = 4.4) than the mean unpleasantness rating for lowest pain intensity level at baseline.

The mean pain unpleasantness ratings at the usual pain intensity level provided by enrolled (mean = 9.7 cm, sd = 3.1), evaluable (mean = 9.6 cm, sd = 3.2), and non-evaluable patients (mean = 10.0 cm, sd = 2.9) at baseline were similar. Results from an independent samples t-test ($t = -0.57$, $df = 122$, $p = 0.56$) showed that the mean pain unpleasantness ratings at usual pain intensity level between evaluable and non-evaluable patients were not statistically different at baseline. Results from a paired-samples t-test ($t = 7.09$, $df = 83$, $p < 0.01$) showed that the mean pain unpleasantness rating provided by evaluable patients for usual pain intensity level at follow-up (mean = 7.2, sd = 3.4) was significantly lower (mean difference = 2.3 cm, sd = 3.0) than the mean unpleasantness rating for usual pain intensity level at baseline. Internal consistency reliability of the items used to form the pain unpleasantness construct at baseline (Cronbach's $\alpha = 0.81$) and follow-up (Cronbach's $\alpha = 0.83$) was adequate.

Table 4.17 Means and Standard Deviations for Items Assessing Highest, Lowest, and Usual Pain Unpleasantness (PU) Levels for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Pain Unpleasantness (PU) at various levels of Pain Intensity (PI) VAS[g] – 15 cm	Enrolled Patients[d] n = 124 Baseline Scores	Evaluable Patients[e] n = 84 Baseline Scores	Non-Evaluable Patients[f] n = 40 Baseline Scores	Evaluable Patients[e] n = 84 Follow-up Scores
PU at Highest PI[a]				
Mean	12.9	12.8*	13.3	11.0*
SD	1.9	2.1	1.5	3.2
PU at Lowest PI[b]				
Mean	6.8	6.5	7.4	4.0
SD	4.2	4.4	3.8	3.5
PU at Usual PI[a]				
Mean	9.7	9.6*	10.0	7.2*
SD	3.1	3.2	2.9	3.4

[a] Indicate along the scale below how unpleasant or disturbing your pain was when it was at its **highest intensity** during the past week.
[b] Indicate along the scale below how unpleasant or disturbing your pain was when it was at its **lowest intensity** during the past week.
[c] Indicate along the scale below how unpleasant or disturbing your pain was when it was at its **usual intensity** during the past week.
[d] All patients enrolled in the study at baseline excluding outliers
[e] All patients who completed baseline and follow-up assessments excluding outliers
[f] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
[g] VAS – 15cm – Visual Analogue Scale, length 15 centimeters
VAS Anchors: 0 cm – Not bad at all, 15cm – The most intense bad feeling possible
* $p < 0.01$

4.3.5 Pain Suffering (PS)

Pain suffering was defined as "Stage III" of the stages of pain model. The pain suffering construct was composed of negative emotion items and negative belief items.

4.3.5.1 Negative Emotions

The following negative emotions were evaluated: depression, anxiety, frustration, anger, and fear. During the interview at baseline and follow-up, patients were asked to indicate the intensity of each negative emotion as it related to their pain in the previous week on visual analogue scale (length = 15cm). The

anchors for the scales assessing each emotion were: “none” and “the most severe imaginable.”

Table 4.18 presents mean ratings for each of the negative emotions and the corresponding standard deviations for enrolled, evaluable, and non-evaluable patients.

The mean rating for all enrolled patients on the depression scale was 9.0 cm (sd = 4.4). Results from an independent samples t-test ($t = -2.58$, $df = 122$, $p = 0.01$) showed that the mean rating on the depression scale from evaluable patients (mean = 8.3 cm, sd = 4.5) was significantly lower than the mean depression rating from non-evaluable patients (mean = 10.5 cm, sd = 3.9) at baseline. Results from a paired-samples t-test ($t = 2.73$, $df = 83$, $p < 0.01$) showed that the mean depression rating provided by evaluable patients at follow-up (mean = 7.08, sd = 4.3) was significantly lower (mean difference = 1.2 cm, sd = 4.23) than the mean depression rating at baseline.

The mean rating for all enrolled patients on the anxiety scale was 9.1 cm (sd = 4.2). Results from an independent samples t-test ($t = -2.32$, $df = 122$, $p = 0.02$) showed that the mean rating on the anxiety scale provided by evaluable patients (mean = 8.5 cm, sd = 4.3) was significantly lower than the mean anxiety rating provided by non-evaluable patients (mean = 10.3 cm, sd = 3.5). Results from a paired-samples t-test ($t = 4.20$, $df = 83$, $p < 0.01$) showed that the mean anxiety rating provided by evaluable patients at follow-up (mean = 6.7 cm, sd = 4.1) was significantly lower (mean difference = 1.7 cm, sd = 3.8) than the mean anxiety rating at baseline.

The mean rating for all enrolled patients on the frustration scale was 11.1 cm (sd = 3.1). Results from an independent samples t-test ($t = -2.19$, $df = 122$, $p = 0.03$) showed that the mean frustration rating from evaluable patients (mean = 10.7 cm, sd = 3.3) was significantly lower than the mean frustration rating from non-evaluable patients (mean = 12.0 cm, sd = 2.5). Results from a paired-samples t-test ($t = 4.80$, $df = 83$, $p < 0.01$) showed that the mean frustration rating

provided by evaluable patients at follow-up (mean = 8.6 cm, sd = 3.9) was significantly lower (mean difference = 2.0 cm, sd = 3.8) than the mean frustration rating at baseline.

The mean rating for all enrolled patients on the anger scale was 8.6 cm (sd = 4.8). Results from an independent samples t-test ($t = -3.0$, $df = 122$, $p < 0.01$) showed that the mean anger rating from evaluable patients (mean = 7.7 cm, sd = 5.0) was significantly lower than the mean anger rating from non-evaluable patients (mean = 10.4 cm, sd = 3.6). Results from a paired-samples t-test ($t = 4.83$, $df = 83$, $p < 0.01$) showed that the mean anger rating provided by evaluable patients at follow-up (mean = 5.4 cm, sd = 4.5) was significantly lower (mean difference = 2.2 cm, sd = 3.8) than the mean anger rating at baseline.

The mean rating for all enrolled patients on the fear scale was 6.6 cm (sd = 4.8). Results from an independent samples t-test ($t = -1.6$, $df = 122$, $p = 0.09$) showed that the mean fear rating from evaluable patients (mean = 6.1 cm, sd = 4.9) was not significantly different than the mean fear rating from non-evaluable patients (mean = 7.7 cm, sd = 3.6). Results from a paired-samples t-test ($t = 1.96$, $df = 83$, $p = 0.05$) showed that the mean fear rating provided by evaluable patients at follow-up (mean = 5.2 cm, sd = 4.4) was significantly lower (mean difference = 0.9 cm, sd = 4.5) than the mean fear rating at baseline. Internal consistency reliability of the items used to form the negative emotions construct at baseline (Cronbach's $\alpha = 0.84$) and follow-up (Cronbach's $\alpha = 0.91$) was adequate.

Table 4.18 Means and Standard Deviations for Items Assessing Negative Emotions for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Negative Emotions VAS[e] – 15 cm	Enrolled Patients[b] n = 124 Baseline Scores	Evaluable Patients[c] n = 84 Baseline Scores	Non-Evaluable Patients[d] n = 40 Baseline Scores	Evaluable Patients[c] n = 84 Follow-up Scores
Depression[a]				
Mean	9.0	8.3*	10.5	7. 0*
SD	4.4	4.5	3.9	4.3
Anxiety[a]				
Mean	9.1	8.5*	10.3	6.7*
SD	4.2	4.3	3.5	4.1
Frustration[a]				
Mean	11.1	10.7*	12.0	8.6*
SD	3.1	3.3	2.5	3.9
Anger[a]				
Mean	8.6	7.7*	10.4	5.4*
SD	4.8	5.0	3.6	4.5
Fear[a]				
Mean	6.6	6.1†	7.7	5.2†
SD	4.8	4.9	4.6	4.4

[a]What kind of negative feelings accompany your pain? Check along each scale below the intensity of each feeling as it has related to your pain over the past week
[b]All patients enrolled in the study at baseline excluding outliers
[c]All patients who completed baseline and follow-up assessments excluding outliers
[d]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
[e]VAS – 15cm – Visual Analogue Scale, length 15 centimeters
VAS Anchors: 0 cm – None, 15cm – The most severe imaginable
*$p < 0.01$
†$p < 0.05$

4.3.5.2 Negative Beliefs

Negative beliefs were assessed through four items. During the interview at baseline and follow-up, patients were asked to indicate along a visual analogue scale (length = 15cm) with anchors, the extent to which they believed that pain interfered in their life, the extent to which patients could endure pain and control pain, and the extent to which patients believed that pain will be removed or cured.

Table 4.19 presents mean ratings for each of the negative beliefs and the corresponding standard deviations for enrolled, evaluable, and non-evaluable patients.

The mean ratings on the scale assessing pain interference provided by enrolled (mean = 11.9 cm, sd = 2.6), evaluable (mean = 11.9 cm, sd = 2.5), and non-evaluable patients (mean = 11.8 cm, sd = 2.7) at baseline were similar. Results from an independent samples t-test ($t = 0.32$, $df = 122$, $p = 0.74$) showed that the mean rating on the scale assessing pain interference provided by evaluable patients was not significantly different from the mean rating provided by non-evaluable patients. Results from a paired-samples t-test ($t = 7.05$, $df = 83$, $p < 0.01$) showed that the mean rating on the scale assessing pain interference provided by evaluable patients at follow-up (mean = 9.3, sd = 3.1) was significantly lower (mean difference = 2.6 cm, sd = 3.4) than the mean rating on the scale assessing pain interference at baseline.

The mean ratings on the scale assessing ability to endure pain provided by enrolled (mean = 11.3 cm, sd = 2.8), evaluable (mean = 11.0 cm, sd = 3.0), and non-evaluable patients (mean = 11.8 cm, sd = 2.4) at baseline were similar. Results from an independent samples t-test ($t = -1.30$, $df = 122$, $p = 0.19$) showed that the mean rating on the scale assessing ability to endure pain provided by evaluable patients was not significantly different from the mean rating provided by non-evaluable patients. Results from a paired-samples t-test ($t = 6.02$, $df = 83$, $p < 0.01$) showed that the mean rating on the scale assessing ability to endure pain provided by evaluable patients at follow-up (mean = 8.8, sd = 3.6) was significantly lower (mean difference = 2.2 cm, sd = 3.4) than the mean rating on the scale assessing ability to endure pain at baseline.

The mean rating for all enrolled patients on the scale assessing ability to control pain was 6.2 cm (sd = 3.4). Results from an independent samples t-test ($t = 2.27$, $df = 122$, $p = 0.02$) showed that the mean rating on the scale assessing ability to control pain provided by evaluable patients (mean = 6.7 cm, sd = 3.5) was significantly

higher than the mean rating on the scale assessing ability to control pain provided by non-evaluable patients (mean = 5.2 cm, sd = 2.9). Results from a paired-samples t-test ($t = -4.25$, $df = 83$, $p < 0.01$) showed that the mean rating on the scale assessing ability to control pain provided by evaluable patients at follow-up (mean = 8.5 cm, sd = 3.2) was significantly higher (mean difference = 1.8 cm, sd = 4.0) than the mean rating provided at baseline.

The mean ratings on the scale assessing the belief that pain will be removed or cured provided by enrolled (mean = 6.2 cm, sd = 4.4), evaluable (mean = 6.2 cm, sd = 4.1), and non-evaluable patients (mean = 6.3 cm, sd = 4.9) at baseline were similar. Results from an independent samples t-test ($t = -0.02$, $df = 122$, $p = 0.97$) showed that the mean rating on the scale assessing the belief that pain will be removed or cured provided by evaluable patients was not significantly different from the mean rating provided by non-evaluable patients. Results from a paired-samples t-test ($t = -0.72$, $df = 83$, $p = 0.14$) showed that the mean rating on the scale assessing the belief that pain will be removed or cured provided by evaluable patients at follow-up (mean = 7.01, sd = 4.1) was not significantly different than the mean rating on the scale assessing the belief that pain will be removed or cured at baseline.

Internal consistency reliability of the items used to form the negative beliefs construct at baseline (Cronbach's $\alpha = 0.36$) was very low. Concbach's α for the same items at follow-up was 0.70.

A possible explanation for the low reliability values is misinterpretation of the scale. The item which assessed ability to control pain had the following anchors: 0 cm - 0% I cannot reduce it at all, and 15 cm – 100% I can reduce it completely. Some patients may have misinterpreted zero percent as the ability to reduce pain to zero.

Some patients may have misinterpreted the item assessing the belief that pain may be removed or cured. In some instances, patients may have provided a rating on the hope or expectation that Avinza would provide significant relief. These discrepancies may have contributed to low reliability scores.

Table 4.19 Means and Standard Deviations for Items Assessing Negative Beliefs for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Negative Beliefs VAS[h] – 15 cm	Enrolled Patients[e] n = 124 Baseline Scores	Evaluable Patients[f] n = 84 Baseline Scores	Non-Evaluable Patients[g] n = 40 Baseline Scores	Evaluable Patients[f] n = 84 Follow-up Scores
Pain Interference[a]				
Mean	11.9	11.9 *	11.8	9.3 *
SD	2.6	2.5	2.7	3.1
Ability to Endure Pain[b]				
Mean	11.3	11.0 *	11.8	8.8 *
SD	2.8	3.0	2.4	3.6
Ability to Control Pain[c]				
Mean	6.2	6.7 *	5.2	8.5 *
SD	3.4	3.5	2.9	3.2
Belief that Pain Will be Removed/Cured[d]				
Mean	6.2	6.2	6.3	7.0
SD	4.4	4.1	4.9	4.1

[a]Indicate along the scale below how: how much does your pain prevent your from doing what you want to do? Scale Anchors: 0 cn - No interference and 15cm - Complete Interference – Cannot do anything

[b]Indicate along the scale below how difficult is it to endure the pain over time? Scale Anchors: 0cm - Not difficult at all and 15 cm - The most difficult imaginable

[c]Indicate along the scale below how much can you reduce the intensity of your pain if you want? Scale Anchors: 0 cm - zero percent, I cannot reduce it all and 15 cm - 100 percent, I can reduce it completely

[d]Indicate along the scale below how likely do you feel that your pain will be removed or cured? Scale Anchors: 0 cm - Impossible and 15 cm - Certain.

[e]All patients enrolled in the study at baseline excluding outliers

[f]All patients who completed baseline and follow-up assessments excluding outliers

[g]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

[h]VAS – 15cm – Visual Analogue Scale, length 15 centimeters

* $p < 0.01$

4.3.6 Pain Behaviors (PB)

Pain behavior was assessed through five subscales that were adapted from the Psychosocial Pain Inventory.[298] The following aspects of pain behavior and their frequency were assessed: "pain behavior" in the home, "social reinforcement for pain behavior," "home or family related responsibilities that were disrupted," "pain contingent down time," and "interview behavior."

A total score that ranges from zero to three was calculated for each of the five items listed above. The score for each item was calculated by summing the number of points associated with every sub-item endorsed by the patient (Appendix D). The total score for each item is then converted to a scaled score (range – 0 to 3).

4.3.6.1 Pain Behavior at Home

Pain behavior at home was assessed by asking patients about the pain behaviors they display at home. During the interview, patients were presented with a list of pain behaviors and were asked about the frequency with which they engaged in the endorsed pain behaviors. Pain behavior scores were calculated as follows:

> Pain behavior - First add up the points associated with the behaviors checked, and then use this sum to a figure a rating as follows (0 to 3)[299]:
>
> 0 = 0 to 4 points
> 1 = 5 to 9 points
> 2 = 10 to 14 points
> 3 = 15 or more points

Table 4.20 presents the frequency distribution and descriptive statistics for the item which assessed pain behaviors at home for enrolled, evaluable, and non-evaluable patients at baseline and follow-up. A higher score on this item implies a greater frequency of pain behaviors.

[298] Getto CJ, Heaton RK. Psychosocial Pain Inventory. Psychological Assessment Resources. Lutz, FL. 1995.
[299] Ibid

A very small proportion of enrolled (4.0%, n = 5), evaluable (4.8%, n = 4) and non-evaluable patients (2.5%, n = 5) scored a zero on the item which assessed frequency of pain behaviors at home. The proportion of evaluable patients (9.5%, n = 8) who scored a zero (0) on this item almost doubled at follow-up. The proportion of evaluable patients (34.5%, n = 29) who received a score of one (1) on the item which assessed pain behaviors at home was nearly twice the proportion of non-evaluable patients (17.5%, n = 7) who received a score of one (1) on this item at baseline. The total number of evaluable patients (n = 36, 42.8%) who received a score of one on the same item increased at follow-up. Although a greater number of evaluable patients at follow-up (n = 25, 29.8%) in comparison with baseline (n = 20, 23.8%) received a score of two (2) on the item which assessed pain behavior at home, more than twice the proportion of patients received a score of three (3) at baseline (36.9%, n = 31) than at follow-up (17.9%, n = 15). A score of three (3) represented the category with the highest frequency of pain behaviors at home.

Results from an independent samples t-test ($t = -1.74$, $df = 122$, $p = 0.08$) showed that baseline mean score on the item which assessed pain behavior at home for evaluable patients (mean = 1.92 sd = 0.9) was not significantly different from the mean score for non-evaluable patients (mean = 2.23, sd = 0.8) at the 95 percent confidence level. Results from a paired-samples t-test ($t = 3.99$, $df = 83$, $p < 0.01$) showed that the mean score provided by evaluable patients at follow-up (mean = 1.55, sd = 0.9) on the item which assessed pain behavior at home was significantly lower than the mean score provided at baseline (mean difference = 0.36 sd = 0.8).

Table 4.20 Frequency Distribution and Descriptive Statistics of Pain Behaviors at Home for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Pain Behavior – Home[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
0	5 (4.0)	4 (4.8)	1 (2.5)	8 (9.5)
1	37 (29.8)	29 (34.5)	7 (17.5)	36 (42.8)
2	33 (26.6)	20 (23.8)	14 (35.0)	25 (29.8)
3	49 (39.5)	31 (36.9)	18 (45.0)	15 (17.9)
Total	124 (99.9*)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	2.0	1.9 *	2.2	1.5 *
SD	0.9	0.9	0.8	0.8

* Total does not equal 100 due to rounding error

[a] "When you are at home and the pain is really bad, how can your family tell that you hurt that way?" Check each pain behavior which occurs with the frequency indicated. Patients who live alone will be assigned a "0."

- ❑ Hold or grasp the area that hurts, 3 times a day or more =1
- ❑ Wince or cringe, 3 times a day or more =2
- ❑ Call a doctor, once a month or more = 3
- ❑ Cry, once a week or more = 3
- ❑ Moan, once a week or more = 3
- ❑ Say it hurts, once a day or more. Ask how this is done, and specify whether it is done with
  - ❑ no affect = 1
  - ❑ some affect = 2
  - ❑ much affect = 3
- ❑ Pace, three times a week or more = 2
- ❑ Go into another room by self, 3 times a week or more = 2
- ❑ Lie down more than once a day = 2
  If this happens at work too with any frequency = 3
- ❑ Sit down, more than 3 times per day = 1
- ❑ Change position frequently = 0
- ❑ Scream, if at all = 3
- ❑ Take medications = 0 (unless addicted; then =3)
- ❑ Ask for help with things that patient would normally be able to do himself/herself, once a day or more = 3
- ❑ Gets angry or irritable, 3 times per week or more = 2

Other (specify): _____

[b] All patients enrolled in the study at baseline excluding outliers

[c] All patients who completed baseline and follow-up assessments excluding outliers

[d] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

0 = 0 to 4 points, 1 = 5 to 9 points, 2 = 10 to 14 points, 3 = 15 or more points

Higher score implies greater frequency of pain behaviors at home

* $p < 0.01$

4.3.6.2 Social Reinforcement for Pain Behavior

Social reinforcement for pain behavior was assessed by asking patients about the response of family members to their behaviors. During the interview, patients were presented with a list of responses and were asked about the frequency with which family members responded to the items endorsed. Social reinforcement for pain behavior scores were calculated as follows:

> Social reinforcement for pain behavior - First add up points associated with checked responses, and then use the sum to figure the rating as follows (0 to 3)[300]:
>
> 0 = 0 to 3 points
> 1 = 4 to 7 points
> 2 = 8 to 11 points
> 3 = 12 or more points

Table 4.21 presents the frequency distribution and descriptive statistics for the item which assessed social reinforcement of pain behavior for enrolled, evaluable, and non-evaluable patients at baseline and follow-up. A higher score on this item implies a greater frequency of social reinforcement.

A majority of enrolled patients (54.0%, n =67), evaluable patients at baseline (56.0%, n = 47) and follow-up (61.9%, n = 52), and non-evaluable patients (50.0%, n = 20) received a score of zero (0) on the item which assessed social reinforcement for pain behavior. The distribution of patients who received a score of one (1) on the item which assessed social reinforcement for pain behavior was as follows: enrolled patient (33.1%, n = 41), evaluable patients at baseline (32.1%, n =27) and follow-up (27.4%, n =23), and non-evaluable patients (35.0%, n = 14). As compared to evaluable patients at baseline (n = 10, 11.9%), one less patient received a score of two (2) on the item which assessed social reinforcement for pain behavior at follow-up (n = 9, 10.7%). None of the evaluable patients at either baseline (n = 0) or

[300] Ibid

follow-up (n = 0) received a score of three on the item which assessed social reinforcement for pain behavior.

Results from an independent samples t-test (t = -0.82, df = 122, p = 0.41) showed that baseline mean score on the item which assessed social reinforcement for pain behavior provided by evaluable patients (mean = 0.5 sd = 0.7) was not significantly different from the mean score for non-evaluable patients (mean = 0.6, sd = 0.7) at the 95 percent confidence level. Results from a paired-samples t-test (t = 1.75, df = 83, p = 0.08) showed that the mean score provided by evaluable patients at follow-up (mean = 0.48, sd = 0.6) on the item which assessed social reinforcement for pain behavior was not significantly different than the mean score provided at baseline (mean difference = 0.07 sd = 0.37).

Table 4.21 Frequency Distribution and Descriptive Statistics of Social Reinforcement of Pain Behavior for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Social Reinforcement[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
0	67 (54.0)	47 (56.0)	20 (50.0)	52 (61.9)
1	41 (33.1)	27 (32.1)	14 (35.0)	23 (27.4)
2	15 (12.1)	10 (11.9)	5 (12.5)	9 (10.7)
3	1 (0.8)	0 (0.0)	1 (2.5)	0 (0.0)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	0.6	0.5	0.6	0.4
SD	0.7	0.7	0.7	0.6

a Ask in relation to the pain behaviors considered generally: "When other family members see you doing these things, and hurting especially badly, how do they respond to you?" Again, ask about any response that is not mentioned spontaneously, determine the general frequency with which each response occurs, and check each response that occurs with the frequency indicated.

- ❑ Express sympathy verbally, daily or almost everyday = 2
- ❑ Withdraws from patient, daily or almost everyday = 0 (unless MMPI-SI 60; then = 2)
- ❑ Encourages patient to take remedial action (i.e., to take meds, lie down, apply heating pad, call doctor, etc.) daily or almost every day = 1
- ❑ Helps patient take remedial action (i.e., gets the meds or heating pad, draws bath, calls doctor, etc) daily or almost everyday = 2
- ❑ Actually administers remedial medication (i.e., gives back rub, holds patient, gives injection, etc.) daily or almost every day = 3
- ❑ Offers to do whatever work the patient is either attempting to do or scheduled to do, when this is something the patient usually feels capable of doing, daily or almost every day = 3
- ❑ Complains = 0
- ❑ Does nothing (ignores patient) = 0
- ❑ Other (specify): _____

[b]All patients enrolled in the study at baseline excluding outliers

[c]All patients who completed baseline and follow-up assessments excluding outliers

[d]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

0 = 0 to 3 points, 1 = 4 to 7 points, 2 = 8 to 11 points, 3 = 12 or more points

4.3.6.3 Home or Family Related Responsibilities

Effect of pain on home and family related responsibilities was assessed by asking patients about their responsibilities before the pain problem and in their current state. During the interview, patients were asked to indicate whether the extent to which they performed responsibilities prior to the pain was "less now" or "never performed now." The score for this item was calculated as follows:

> Home or family related responsibilities - Give one point for each previously discharged responsibility that is done less now, and two points for each which is never done now. Add the points and use the sum to figure out a rating as follows (0 to 3)[301]:
>
> 0 = 0 points
> 1 = 1 or 2 points
> 2 = 3 to 6 points
> 3 = 7 or more points

Table 4.22 presents the frequency distribution and descriptive statistics for the item which assessed the effect of pain on home and family related responsibilities for enrolled, evaluable, and non-evaluable patients at baseline and follow-up. A higher score on this item implies a greater reduction in home or family related responsibilities.

A very small proportion of enrolled patients (6.5%, n = 8) and evaluable patients at baseline (9.5%, n = 8) patients at baseline received a score of zero on the item which assessed the effect of pain on home and family related responsibilities. The proportion of evaluable patients (6.0%, n = 5) who received this score at follow-up declined. The number of evaluable patients who received a score of one (1) on this item increased from baseline (n = 9, 10.7%) to follow-up (n = 12, 14.2%). None of the patients in the non-evaluable group (n = 0) received a score of either zero (0) or one (1). A large majority of non-evaluable patients (n = 35, 87.5%) received a score of three (3), which suggested that these patients experienced the highest level of

[301] Ibid

reduction in home and family related responsibilities due to their pain. A majority of evaluable patients at baseline (61.9%, n = 52) and follow-up (51.2%, n = 43) experienced a similar level of reduction in home and family related responsibilities

Results from an independent samples t-test ($t = -3.38$, $df = 122$, $p < 0.01$) showed that baseline mean score on the item which assessed the effect of pain on home or family related responsibilities for evaluable patients (mean = 2.3, sd = 1.0) was significantly lower than the mean score for non-evaluable patients (mean = 2.8, sd = 0.3) at the 95 percent confidence level. Results from a paired-samples t-test ($t = 1.09$, $df = 83$, $p = 0.27$) showed that the mean score provided by evaluable patients at follow-up (mean = 2.2, sd = 0.8) on the item which assessed effect of pain on home and family related responsibilities was not significantly different than the mean score provided at baseline (mean difference = 0.1, sd = 0.3).

Table 4.22 Frequency Distribution and Descriptive Statistics of Home or Family Related Responsibilities for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Home or Family Related Responsibilties[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
0	8 (6.5)	8 (9.5)	0 (0.0)	5 (6.0)
1	9 (7.3)	9 (10.7)	0 (0.0)	12 (14.2)
2	20 (16.1)	15 (17.9)	5 (12.5)	24 (28.6)
3	87 (70.2)	52 (61.9)	35 (87.5)	43 (51.2)
Total	124 (100.1[*])	84 (100.0)	40 (100.0)	84 100.0)
Mean	2.5	2.3	2.8	2.2
SD	0.8	1.0	0.3	0.8

[*]Total does not equal 100 due to rounding error

[a]Use the following checklist to indicate what home or family related responsibilities the patient discharged prior to the pain problem as compared to now. Under ***"*** *Before"* check only those activities that the patient did at least half of the time before (i.e., it must have been primarily the patient's responsibility – not mostly someone else's in the family). Check under ***"Less now"*** if, due to the pain, the frequency with which the patient does the activity has decreased but by no more than 50 percent. Check under *"Never now"* if the frequency has decreased by more than 50 percent. Give one point for each previously discharged responsibility that is done less now, and two points for each which is never done now. Add the points and use the sum to figure out a rating as follows (0 to 3):

Responsibility	Before	Less Now	Never Now
Housecleaning	_____	_____	_____
Clothes washing	_____	_____	_____
Clothes ironing	_____	_____	_____
Shopping	_____	_____	_____
Cooking	_____	_____	_____
Repair work (home)	_____	_____	_____
Repair work (car)	_____	_____	_____
Yard work	_____	_____	_____
Errands	_____	_____	_____
Caring for children	_____	_____	_____
Disciplining children	_____	_____	_____
Driving other family members	_____	_____	_____
Family finances	_____	_____	_____
Family correspondence	_____	_____	_____
Other (specify):			

[b]All patients enrolled in the study at baseline excluding outliers

[c]All patients who completed baseline and follow-up assessments excluding outliers

[d]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

0 = 0 to 3 points, 1 = 4 to 7 points, 2 = 8 to 11 points, 3 = 12 or more points

4.3.6.4 Pain Contingent Down Time

Pain contingent down time was assessed by asking patients to indicate the amount of time they spend laying down because of their pain. The following categories were formed to calculate scores:

0 = No more than 1 hour/day	2 = Two to four hours/day
1 = > one and < two hours/day	3 = Greater than four hours/day

Table 4.23 presents the frequency distribution and descriptive statistics for the item which assessed pain contingency down time for enrolled, evaluable, and non-evaluable patients at baseline and follow-up. A higher score on this item implies a greater amount time that patients spend lying down due to pain.

The distribution of patients who reported that they spend less than one hour per day lying down was as follows: enrolled patients (n =21, 16.9%), evaluable patients at baseline (n = 16, 19.0%) and follow-up (n = 15, 17.9%), and non-evaluable patients (n = 5, 12.5%). The total number of evaluable patients who reported that they spend greater than one but less than two hours per day lying down was 16 (19.0%) at baseline and 17 at follow-up (20.2%). The proportion of enrolled patients (37.1%, n = 46), evaluable patients (36.9%, n = 31), and non-evaluable patients (37.5%, n = 15) who spend greater than four hours per day lying down at baseline was similar. A smaller proportion of evaluable patients at follow-up (23.8%, n = 20) spend as much time lying down because of their pain.

Results from an independent samples t-test ($t = -1.06$, $df = 122$, $p = 0.28$) showed that baseline mean score on the item which assessed pain contingent down time for evaluable patients (mean = 1.82 sd = 1.1) was not significantly different from the mean score for non-evaluable patients (mean = 2.05, sd = 0.9) at the 95 percent confidence level. Results from a paired-samples t-test ($t = 1.23$, $df = 83$, $p = 0.22$) showed that the mean score provided by evaluable patients at follow-up (mean = 1.67, sd = 1.0) on the item which assessed pain contingency down time was not

significantly different than the mean score provided at baseline (mean difference = 0.15 sd = 0.8).

Table 4.23 Frequency Distribution and Descriptive Statistics of Pain Contingent Down Tine for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Pain Contingent Down Time[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
0	21 (16.9)	16 (19.0)	5 (12.5)	15 (17.9)
1	19 (15.3)	16 (19.0)	3 (7.5)	17 (20.2)
2	38 (30.6)	21 (25.0)	17 (42.5)	32 (38.1)
3	46 (37.1)	31 (36.9)	15 (37.5)	20 (23.8)
Total	124 (100.1*)	84 (99.9*)	40 (100.0)	84 (100.0)
Mean	1.8	1.8	2.0	1.6
SD	1.1	1.1	0.9	1.0

* Total does not equal 100 due to rounding error
a Determine about how many daytime hours are spent lying sown because of pain these days?
Less than one hour per day = 0
Greater than one but less than two hours per day = 1
Two to four hours per day = 2
More than four hours per day = 3
b All patients enrolled in the study at baseline excluding outliers
c All patients who completed baseline and follow-up assessments excluding outliers
d All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

4.3.6.5 Observed Pain Behaviors

Observed pain behaviors were defined as those behaviors observed by the interviewer during the interview. Various pain behaviors were listed on the data collection sheet. Observed pain behaviors were endorsed on the sheet. The score for observed pain behaviors was calculated as follows:

> Interview behavior: Score is highest rating corresponding to an endorsed item (i.e., the rating of the most dramatic pain behavior); or score 3 points if pain behavior clearly varied with topic being discussed.[302]

[302] Ibid.

Table 4.24 presents the frequency distribution and descriptive statistics for the item which assessed observed pain behaviors for enrolled, evaluable, and non-evaluable patients at baseline and follow-up. The distribution of patients who received a score of zero (0) on the item which assessed observed pain behaviors was as follows: enrolled patients (n = 16, 12.9%), evaluable patients at baseline (n = 12, 14.3%) and follow-up (n = 28, 33.3%), and non-evaluable patients (n = 4, 10.0%). The distribution of patients who received a score of one (1) on the item which assessed observed pain behaviors was as follows: enrolled patients (n = 36, 29.0%), evaluable patients at baseline (n = 22, 26.2%) and follow-up (n = 22, 26.2%), and non-evaluable patients (n = 14, 35.0%). The distribution of patients who received a score of two (2) on the item which assessed observed pain behaviors was as follows: enrolled patients (n = 32, 25.8%), evaluable patients at baseline (n = 22, 26.2%) and follow-up (n = 15, 17.9%), and non-evaluable patients (n = 10, 25.0%). The distribution of patients who received a score of three (3) on the item which assessed observed pain behaviors was as follows: enrolled patients (n = 40, 32.3%), evaluable patients at baseline (n = 28, 33.3%) and follow-up (n = 19, 22.6%), and non-evaluable patients (n = 12, 30.0%).

Results from an independent samples t-test ($t = 0.17$, $df = 122$, $p = 0.85$) showed that the baseline mean score on the item which assessed observed pain behaviors for evaluable patients (mean = 1.79 sd = 1.0) was not significantly different from the mean score for non-evaluable patients (mean = 1.75, sd = 1.0) at the 95 percent confidence level. Results from a paired-samples t-test ($t = 3.40$, $df = 83$, $p < 0.01$) showed that the mean score provided by evaluable patients at follow-up (mean = 1.29, sd = 1.1) on the item which assessed observed pain behavior was significantly lower than the mean score provided at baseline (mean difference = 0.49 sd = 1.3).

Table 4.24 Frequency Distribution and Descriptive Statistics of Observed Pain Behaviors for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Observed Pain Behaviors[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
0	16 (12.9)	12 (14.3)	4 (10.0)	28 (33.3)
1	36 (29.0)	22 (26.2)	14 (35.0)	22 (26.2)
2	32 (25.8)	22 (26.2)	10 (25.0)	15 (17.9)
3	40 (32.3)	28 (33.3)	12 (30.0)	19 (22.6)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	1.7	1.7 *	1.7	1.2 *
SD	1.0	1.0	1.0	1.1

[a]Describe the patient's pain behavior that you observed in the interview:

- ❑ Held or grasped the area that hurt = 1
- ❑ Winced or cringed = 2
- ❑ Moaned = 3
- ❑ Paced = 3
- ❑ Said it hurt, not in direct response to a question or statement by the interview, with
  - ❑ much affect = 3
  - ❑ little affect = 2
  - ❑ some affect = 2
  - ❑ no affect = 1
- ❑ Asked to call doctor = 3
- ❑ Changed position frequently = 1
- ❑ Took medications = 3
- ❑ Became irritable = 2
- ❑ Asked to stop interview = 3
- ❑ No pain behavior was observed = 3 (0 if patient is currently getting very much or total relief from treatment).

Score is highest rating corresponding to an endorsed item (i.e., the rating of the most dramatic pain behavior); or score 3 points if pain behavior clearly varied with topic being discussed.[303]

[b]All patients enrolled in the study at baseline excluding outliers

[c]All patients who completed baseline and follow-up assessments excluding outliers

[d]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

* $p < 0.01$

[303] Ibid.

4.3.7 Digit Span Test (DST)

The digit span test consists of two subtests, the digits span forwards and backwards. In the digits forward test, subjects are required to repeat the numbers in the same sequence as the examiner. Eight sequences of numbers are presented, with sequences ranging from two to nine numbers. For each sequence, two trials are presented. The procedure is followed until the patient fails to correctly repeat two trials of the same sequence. Total score is the number of sequences correctly repeated.

Table 4.25 presents the frequency distributions and descriptive statistics of the digits forward and backward test for enrolled, evaluable, and non-evaluable patients at baseline and follow-up.

The distribution of patients who received a raw score ranging from one to four on the digits forward test was as follows: enrolled patients (n = 1, 0.8%), evaluable patients at baseline (n = 1, 1.2%) and follow-up (n = 0, 0.0%), and non-evaluable patients (n = 0, 0.0%). The distribution of patients who received a raw score ranging from five to eight on the digits forward test was as follows: enrolled patients (n = 46, 37.1%), evaluable patients at baseline (n = 28, 33.3%) and follow-up (n = 24, 28.5%), and non-evaluable patients (n = 18, 45.0%). An equal number (n = 47, 56.0%) of evaluable patients at baseline and follow-up obtained a score on the digits forward test that ranged from nine to twelve.

Results from an independent samples t-test ($t = 0.56$, $df = 122$, $p = 0.57$) showed that the mean score of evaluable patients on the digits span forward test at baseline (mean = 9.42, sd = 2.2) was not significantly different from that of non-evaluable patients (mean = 9.17, sd = 2.6). Results from a paired-samples t-test ($t = 4.31$, $df = 83$, $p < 0.01$) showed that the mean score of evaluable patients on the digits span forward test at follow-up (mean = 10.20, sd = 2.3) was significantly greater than that at baseline (mean difference = 0.77, sd = 1.6).

Participants can receive a maximum score of 16 on the digits forward test. Average span in the normal population is 6 (sd = 1.0). Patients with a span that is five or greater are considered to have a normal span of attention, a span of 4 is indicative of

borderline impairment, and a span of 3 indicates impairment.[304] A mean score of 9.42 indicates that the average span among evaluable patients at baseline was in the four to five range. At follow-up, the span was slightly above five.

For the digits span backward test, participants are expected to recall presented numbers in the reverse order. Seven sequences of numbers are presented, with sequences ranging from two to eight numbers. Total score is the number of sequences correctly repeated. Participants can receive a maximum score of 14 on this test.

Results from table 4.25 showed that the number of evaluable patients who received a score of one to four on the digits backward test at baseline (n = 8, 9.5%) was twice that at follow-up (n = 4, 4.8%). The distribution of patients who received a raw score ranging from five to eight on the digits backward test was as follows: enrolled patients (n = 89, 71.8%), evaluable patients at baseline (n = 63, 75.0%) and follow-up (n = 57, 67.9%), and non-evaluable patients (n = 26, 65.0%). The proportion of evaluable patients who received a raw score ranging from nine to twelve on the digits backward test increased from baseline (n = 13, 15.5%) to follow-up (n =21, 25.0%)

Results from an independent samples t-test ($t = 0.98$, $df = 122$, $p = 0.32$) showed that the mean score of evaluable patients on the digits span backward test at baseline (mean = 6.72, sd = 1.8) was not significantly different from that of non-evaluable patients (mean = 6.32, sd = 2.5). Results from a paired-samples t-test ($t = 3.34$, $df = 83$, $p < 0.01$) showed that the mean score of evaluable patients on the digits span backward test at follow-up (mean = 7.40, sd = 2.1) was significantly greater than that at baseline (mean difference = 0.67, sd = 1.8). The test-retest reliability coefficients for the digit span forward and backward tests were 0.74 and 0.58 respectively.

[304] Ibid

Table 4.25 Frequency Distribution and Descriptive Statistics of Digit Span Test for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Digit Span Test	Enrolled Patients[c] n (%) Baseline Scores	Evaluable Patients[d] n (%) Baseline Scores	Non-Evaluable Patients[e] n (%) Baseline Scores	Evaluable Patients[d] n (%) Follow-up Scores
Digits Span Forward[a]				
1 to 4	1 (0.8)	1 (1.2)	0 (0.0)	0 (0.0)
5 to 8	46 (37.1)	28 (33.3)	18 (45.0)	24 (28.5)
9 to 12	63 (50.8)	47 (56.0)	16 (40.0)	47 (56.0)
13 to 16	14 (11.3)	8 (9.5)	6 (15.0)	13 (15.5)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	9.3	9.4†	9.1	10.2†
SD	2.3	2.2	2.6	2.3
Digits Span Backward[b]				
1 to 4	14 (11.3)	8 (9.5)	6 (15.0)	4 (4.8)
5 to 8	89 (71.8)	63 (75.0)	26 (65.0)	57 (67.9)
9 to 12	20 (16.1)	13 (15.5)	7 (17.5)	21 (25.0)
13 to 14	1 (0.8)	0 (0.0)	1 (2.5)	2 (2.4)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.1*)
Mean	6.5	6.7†	6.3	7.4†
SD	2.1	1.8	2.5	2.1

*Total does not equal 100 due to rounding error
[a] Digits span forward test – Maximum score is 16 points
[b] Digits span backward test – Maximum score is 14 points
[c] All patients enrolled in the study at baseline excluding outliers
[d] All patients who completed baseline and follow-up assessments excluding outliers
[e] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
† $p < 0.01$

4.3.8 Digit Symbol Test (DSYT)

The test comprises a series of boxes labeled with random numbers ranging from one to nine, along with nine symbols that are also identified by numbers. The subject's task is to copy the appropriate symbol for each corresponding number. Test score is calculated as the total number of symbols that were correctly copied within two minutes. Table 4.26 presents the frequency distribution and descriptive statistics of the digit symbol test for enrolled, evaluable, and non-evaluable patients at baseline and follow-up.

The distribution of patients who received a raw score ranging from one to thirty on the test was as follows: enrolled patients (n = 3, 2.4%), evaluable patients at baseline (n = 1, 1.2%) and follow-up (n = 2, 2.4%), and non-evaluable patients (n = 2, 5.0%). The distribution of patients who received a raw score ranging from 31 to 60 on the digit symbol test was as follows: enrolled patients (n = 61, 49.2%), evaluable patients at baseline (n = 40, 47.6%) and follow-up (n = 32, 38.0%), and non-evaluable patients (n = 21, 52.5%). The distribution of patients who received a raw score ranging from 61 to 90 on the digit symbol test was as follows: enrolled patients (n = 52, 41.9%), evaluable patients at baseline (n = 37, 44.1%) and follow-up (n = 46, 54.8%), and non-evaluable patients (n = 15, 37.5%).

Results from an independent samples t-test ($t = 1.56$, $df = 122$, $p = 0.12$) showed that the mean score of evaluable patients on the digit symbol test at baseline (mean = 62.1, sd = 16.3) was not significantly different from that of non-evaluable patients (mean = 56.9, sd = 18.6). Results from a paired-samples t-test ($t = -3.81$, $df = 83$, $p < 0.01$) showed that the mean score of evaluable patients on the digit symbol test at follow-up (mean = 65.4, sd = 16.3) was significantly greater than that at baseline (mean difference = 3.3, sd = 8.1). The test-retest reliability coefficient for the DSYT test was 0.87.

Table 4.26 Frequency Distribution and Descriptive Statistics of Digit Symbol for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Digit Symbol Test[a]	Enrolled Patients[b] n (%) Baseline Scores	Evaluable Patients[c] n (%) Baseline Scores	Non-Evaluable Patients[d] n (%) Baseline Scores	Evaluable Patients[c] n (%) Follow-up Scores
Digits Symbol Test				
1 to 30	3 (2.4)	1 (1.2)	2 (5.0)	2 (2.4)
31 to 60	61 (49.2)	40 (47.6)	21 (52.5)	32 (38.0)
61 to 90	52 (41.9)	37 (44.1)	15 (37.5)	46 (54.8)
91 to 133	8 (6.5)	6 (7.1)	2 (5.0)	4 (4.8)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	60.4	62.1*	56.9	65.4*
SD	17.2	16.3	18.6	16.3

a Digit symbol test – Maximum score is 133 points
b All patients enrolled in the study at baseline excluding outliers
c All patients who completed baseline and follow-up assessments excluding outliers
d All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
* $p < 0.01$

4.3.9 Paced Auditory Serial Addition Test (PASAT)

The paced auditory serial attention test is a measure of information processing, and sustained attention. Subjects are required to add each successive pair of numbers that that are presented in a sequence of fifty numbers. Two PASAT tests were administered, in which the presentation rate of each number was set at 2.4 and 2.0 seconds. Scores for each test were calculated as the correct number of responses to each test.

Table 4.27 presents the frequency distribution and descriptive statistics of the two PASAT tests. A total of 13 (10.5%) enrolled patients, 6 evaluable patients (7.3%), and 7 non-evaluable patients (17.5%) responded correctly to 40 percent or fewer items on the PASAT 2.4 at baseline. Among evaluable patients, a larger proportion of patients responded correctly to greater than 82 percent of items on the PASAT 2.4 at follow-up (n = 39, 46.4%) as compared to baseline (n = 24, 29.3%).

Results from an independent samples t-test ($t = 1.33$, $df = 114$, $p = 0.18$) showed that the mean score of evaluable patients (mean = 33.7, sd = 9.1) on the PASAT 2.4 was not

significantly different from non-evaluable patients (mean = 31.0, sd = 10.8) at baseline. Results from a paired-samples t-test ($t = -7.15$, $df = 81$, $p < 0.01$) showed that mean score of evaluable patients on PASAT 2.4 at follow-up (mean = 38.4, 9.1) was significantly greater (mean difference = 4.6, sd = 5.9) than at baseline.

The distribution of patients who responded correctly to 40 percent or fewer items on the PASAT 2.0 was as follows: enrolled patients (n = 16, 12.9%), evaluable patients at baseline (n = 8, 9.7%) and follow-up (n = 3, 3.6%), and non-evaluable patients (n = 8, 20%). The distribution of patients who responded correctly to at least 82 percent of the items on the PASAT 2.0 was as follows enrolled patients (n = 23, 18.5%), evaluable patients at baseline (n = 18, 22.0%) and follow-up (n = 32, 38.1%), and non-evaluable patients (n = 5, 12.5%). Results from an independent samples t-test ($t = 2.42$, $df = 114$, $p = 0.01$) showed that the mean score of evaluable patients (mean = 32.8, sd = 9.4) on PASAT 2.0 was significantly higher than non-evaluable patients (mean = 28.09, sd = 9.9) at baseline. Results from a paired sample t-test ($t = -5.64$, $df = 81$, $p < 0.01$) showed that mean score of evaluable patients at follow-up (mean = 36.72, 9.0) on PASAT 2.0 was significantly greater (mean difference = 3.89, sd = 6.2) than that at baseline.

The average score on the PASAT 2.4 and 2.0 tests improved from baseline to follow-up. The test-retest reliability coefficients for the PASAT 2.4 and 2.0 tests were 0.78 and 0.77 respectively.

Table 4.27 Frequency Distribution and Descriptive Statistics of Paced Auditory Serial Addition Test for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up				
Paced Auditory Serial Addition Test	Enrolled Patients[c] n (%) Baseline Scores	Evaluable Patients[d] n (%) Baseline Scores	Non-Evaluable Patients[e] n (%) Baseline Scores	Evaluable Patients[d] n (%) Follow-up Scores
PASAT 2.4[a]				
1 to 10	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
11 to 20	13 (10.5)	6 (7.3)	7 (17.5)	3 (3.6)
21 to 30	39 (31.5)	27 (32.9)	12 (30.0)	16 (19.0)
31 to 40	30 (24.2)	25 (30.5)	5 (12.5)	24 (28.6)
41 to 50	34 (27.4)	24 (29.3)	10 (25.0)	39 (46.4)
Missing	8 (6.4)	2 (2.4)	6 (15.0)	2 (2.4)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	32.9	33.7	31.0	38.4
SD	9.7	9.1	10.8	9.1
PASAT 2.0[b]				
1 to 10	1 (0.8)	1 (1.2)	0 (0.0)	0 (0.0)
11 to 20	15 (12.1)	7 (8.3)	8 (20.0)	3 (3.6)
21 to 30	43 (34.7)	29 (34.5)	14 (35.0)	20 (23.8)
31 to 40	34 (27.4)	27 (32.1)	7 (17.5)	27 (32.1)
41 to 50	23 (18.5)	18 (21.4)	5 (12.5)	32 (38.1)
Missing	8 (6.5)	2 (2.4)	6 (15.0)	2 (2.4)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.0)
Mean	31.4	32.8*	28.0	36.7*
SD	9.7	9.4	9.9	9.0

[a] PASAT 2.4 – Paced Auditory Serial Addition Test with a presentation rate of one number every 2.4 seconds. Maximum score is 50 points

[b] PASAT 2.0 – Paced Auditory Serial Addition Test with a presentation rate of one number every 2.0seconds. Maximum score is 50 points

[c] All patients enrolled in the study at baseline excluding outliers

[d] All patients who completed baseline and follow-up assessments excluding outliers

[e] All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers

* $p < 0.01$

A comparison of PASAT scores from a normal sample and the current sample of evaluable pain patients in Table 4.28 suggested that as age increased performance on the test worsened. Pain patients in all three age groups (16 to 29, 30 to 49, and 50 to 69) had lower mean scores on both the PASAT 2.4 and 2.0 as compared to the normal sample.

These results indicated that as a group, pain patients have a compromised information processing ability and reduced ability to maintain sustained attention.

Table 4.28 Comparison between a Normal Sample and Evaluable Patients at Baseline and Follow-up on the Mean Number of Correct Responses to the PASAT 2.4 and 2.0 by Age Group				
Test	**Study Group**	16-29	30-49	50-69
		Mean (SD)	Mean (SD)	Mean (SD)
PASAT 2.4 [a]	Normal Sample (N = 90)	47.4 (10.1) n = 30	43.4 (10.2) n = 30	43.5 (13.6) n = 30
	Evaluable Patients [c] – Baseline (N = 82)	42 (NA) n = 1	33.2 (9.2) n = 50	34.2 (9.2) n = 31
	Evaluable Patients [c] - Follow-up (N = 82)	45 (NA) n = 1	39.0 (8.9) n = 50	37.2 (9.5) n = 31
PASAT 2.0 [b]	Normal Sample (N = 90)	42.0(12.5) n = 30	41.9 (10.2) n = 30	35.6 (14.6) n = 30
	Evaluable Patients [c] – Baseline (N = 82)	40.0 (NA) n = 1	32.7 (8.4) n = 50	32.8 (11.0) n = 31
	Evaluable Patients [c] - Follow-up (N = 82)	39 (NA) n = 1	37.1 (8.1) n = 50	36.0 (9.7) n = 31

[a]PASAT 2.4 – Paced Auditory Serial Addition Test with a presentation rate of one number every 2.4 seconds. Maximum score is 50 points
[b]PASAT 2.0 – Paced Auditory Serial Addition Test with a presentation rate of one number every 2.0 seconds. Maximum score is 50 points
[c]All patients who completed baseline and follow-up assessments excluding outliers

4.4 Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI) was administered to assess depression. The BDI was originally composed of 22 items. However, for this study the item assessing suicidal ideation was not included. Thus, the total score on the BDI was calculated based on responses to 21 items. Each item on the inventory includes four responses, which are scored from zero to three. Table 4.29 presents the frequency distribution of the sample by categories that enable clinical interpretation of scores.

The distribution of patients who were classified with mild mood disturbance was as follows: enrolled patients (n = 33, 26.6%), evaluable patients at baseline (n = 27, 32.1%) and follow-up (n = 25, 29.8%), and non-evaluable patients (n = 6, 15.0%). A greater proportion of non-evaluable patients (27.5%, n =11) as compared to evaluable patients at baseline (20.2%, n = 17) and follow-up (16.7%, n = 14) were classified with borderline clinical depression.

The distribution of patients who were classified with moderate depression was as follows: enrolled patients (n = 31, 25.0%), evaluable patients at baseline (n = 22, 26.2%) and follow-up (n = 16, 19.0%), and non-evaluable patients (n = 9, 22.5%). The number of non-evaluable patients (n = 12, 30.0%) who were categorized with severe depression was three times the number of evaluable patients (n = 4, 4.8%) in that category at baseline.

Results from an independent samples t-test ($t = -2.67$, $df = 122$, $p < 0.01$) showed that the mean score of evaluable patients (mean = 18.7, sd = 9.0) on the BDI was significantly lower than non-evaluable patients (mean = 23.2, sd = 8.1) at baseline. Results from a paired sample t-test ($t = 5.22$, $df = 83$, $p < 0.01$) showed that the mean score of evaluable patients at follow-up (mean = 14.5, sd = 8.8) was significantly lower (mean difference = 4.2, sd = 7.3) than that at baseline.

Table 4.29 Frequency Distribution and Descriptive Statistics of Beck Depression Inventory for Enrolled, Evaluable, and Non-Evaluable Patients at Baseline and Follow-up

Beck Depression Inventory	Enrolled Patients[a] n (%) Baseline Scores	Evaluable Patients[b] n (%) Baseline Scores	Non-Evaluable Patients[c] n (%) Baseline Scores	Evaluable Patients[b] n (%) Follow-up Scores
These ups and downs are considered normal (0 to 10)	14 (11.3)	12 (14.3)	2 (5.0)	26 (30.9)
Mild mood disturbance (11 to 16)	33 (26.6)	27 (32.1)	6 (15.0)	25 (29.8)
Borderline clinical depression (17 to 20)	28 (22.6)	17 (20.2)	11 (27.5)	14 (16.7)
Moderate depression (21 to 30)	31 (25.0)	22 (26.2)	9 (22.5)	16 (19.0)
Severe depression (31 to 40)	16 (12.9)	4 (4.8)	12 (30.0)	2 (2.4)
Extreme depression (41 or greater)	2 (1.6)	2 (2.4)	0 (0.0)	1 (1.2)
Total	124 (100.0)	84 (100.0)	40 (100.0)	84 (100.1)
Mean	20.21	18.75*	23 .28	14.54*
SD	9.0	9.0	8.1	8.8

[a]All patients enrolled in the study at baseline excluding outliers
[b]All patients who completed baseline and follow-up assessments excluding outliers
[c]All enrolled patients who dropped out of the study or were lost to follow-up excluding outliers
* $p < 0.01$

Results from a multiple regression analysis ($F = 11.21$, $p < 0.001$) showed that items on the negative emotions scale (depression, anxiety, frustration, anger, and fear) explained a third of the variance ($R^2 = 0.32$) in Beck Depression Inventory scores. The "depression" item accounted for 25.4 percent of the variance ($R^2 = 0.25$) in the BDI scores. The results suggest that there is some overalap between BDI scores and the negative emotions scale. The relative ease and quickness with which the negative emotions scale can be administered may justify its use as a supplement to the BDI inclinical settings.

4.5 Structural Equation Modeling

This section of the results chapter addresses the measurement and factor structure of the stages of pain model. A structural equation modeling (SEM) procedure was used to determine fit of the current data to the stages of pain model. An overview of some general modeling conventions is presented below. The stages of pain model will be addressed subsequently

SEM is a statistical technique, which relies on existing information to postulate the causal structure of a given set of data.[305] The methodology serves to confirm relationships between unobserved variables (construct/factor/latent) and items believed to represent it. The latent variable can be measured indirectly through observed phenomena or behaviors, which are referred to as indicators. This procedure is commonly referred to as a confirmatory factor analysis and represents the measurement portion of a SEM. Additionally, relationships between latent variables may be examined. This portion of the model is referred to as the structural model (Figure 4.1).

In Figure 4.1, the variable "F" represents a latent construct. The variables denoted as "V" are observed indicators that load on the latent. The terms labeled "E" refer to measurement error associated with the observed indicators, while "D" represents the disturbance term associated with the regression of one latent on another. The associations modeled in Figure 4.1 may be represented with the following set of equations:

$$F_2 = F_1 + D_2$$

$$V_1 = F_1 + E_1$$

$$V_2 = F_1 + E_2$$

$$V_3 = F_1 + E_3$$

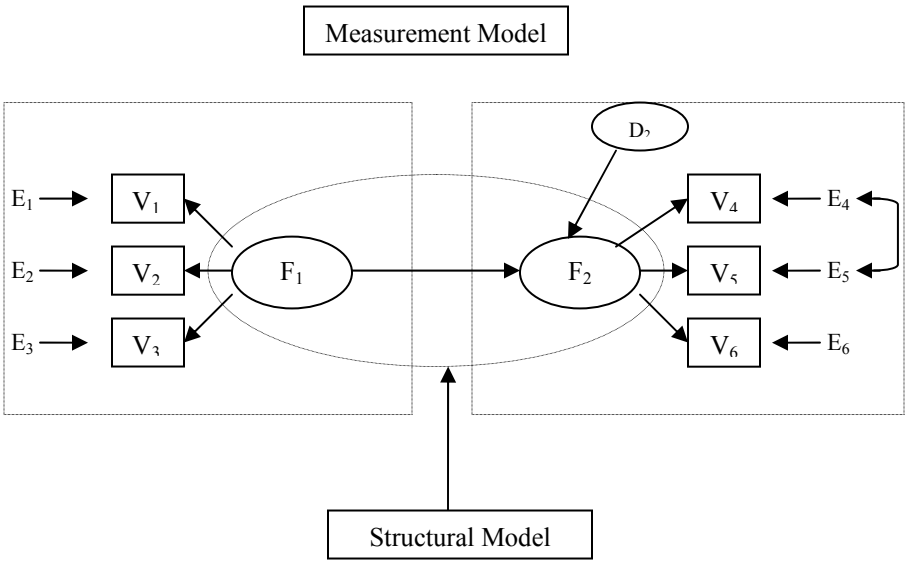
$$V_4 = F_2 + E_4$$

$$V_5 = F_2 + E_5$$

[305] Byrne BM. Structural Equation Modeling with EQS and EQS/Windows. Sage Publications Inc. Thousand Oaks, CA. 1994.

$$V_6 = F_2 + E_6$$

Figure 4.1 – Components of a Structural Equation Model[306]



F_1, F_2 – Unobserved latent variable (factor)

$V_{1 \text{ to}}\ V_6$ – Observed variable

F ⟶ V – Path coefficient for regression of observed variables onto factor

F ⟶ F – Path coefficient for regression of one factor onto another

D ⟶ F – Residual error (disturbance) in prediction of factor

E ⟶ V – Measurement Error Associated with Observed Variable

E ⟷ E – Measurement Error between V_4 and V_5 is correlated

The fit of the hypothesized model to the data is compared with that of the null model (i.e., no structure imposed on the data). Overall model fit is usually determined on the basis of the exact chi-square test. Model modifications may be performed to improve fit to the data.

A non-significant value of the chi-square statistic ($p > 0.05$) indicates that fit of the over-identified model does not differ from fit of the null model, and the hypothesized

[306] Ibid

model is acceptable.[307] In order to adequately assess factor loadings and latent structure of the current model, the following goodness of fit indices were utilized: comparative fit index (CFI), standardized root mean square residual (SRMR), root mean square error of approximation (RMSEA), normed fit index (NFI), and goodness of fit index (GFI).[308] The recommended cutoff values for goodness of fit indices considered for this study are provided in Table 4.30 below[309]:

Table 4.30 Cutoff Values for Fit Indices	
Fit Index	Cutoff Values
Bentler-Bonett Normed Fit Index (NFI)	0.90
Comparative Fit Index (CFI)	0.95
Joreskog-Sorbom Goodness of Fit Index (GFI)	0.95
Standardized Root Mean Square Residual (SRMR)	0.08
Root Mean Square Error of Approximation (RMSEA)	0.06

4.5.1 Overview of Modeling Approach

The overall approach to obtain fit of the stages of pain model (SOPM) to current data is outlined below. The hypothesized (original) SOPM was tested first. This model included all the stages of pain model variables. Since this model did not fit the baseline data adequately, modifications were made to resemble a previously published model. Even though this model fit the baseline data adequately, fit improvements were made by allowing the correlation between errors of two indicators to be estimated freely. However, errors were encountered when this model (i.e., model resembling the previously published SOPM with correlated errors) was fit to follow-up data. Consequently, offending indicators were removed and the model was tested with both baseline and follow-up data. Although the model with correlated errors fit baseline data,

[307] Kline RB. Principles and practice of structural equation modeling. The Gulford Press. New York, NY. 1998.
[308] Hu L, Bentler PM. Fit indices in covariance structure modeling: sensitivity to underparametrized model misspecification. *Psychological Methods*. 1998;3:424-453.
[309] Hu L, Bentler PM. Cutoff criteria for fit indexes in covariance structural analysis: conventional criteria versus new alternatives. *Structural Equation Modeling*. 1999;6:1-55.

the procedure for removing indicators was followed to maintain equality in the measurement and structural portions of the model for both waves of data. Removal of the offending indicators resulted in excellent model fit. In order to assess model reliability, the final model with baseline and follow-up data were subjected to simultaneous constraints.

Adequate reliability enabled the construction of two-wave models, which controlled for autocorrelation between baseline and follow-up data. The subsequent section addresses two-wave models.

4.5.2 Baseline Stages of Pain Model - Original

The original stages of pain model was composed of four latent variables or factors: pain intensity, pain unpleasantness, pain suffering, and pain behaviors. The pain intensity factor was composed of three items, i.e., pain intensity at the highest, lowest and usual levels in the previous week. The pain unpleasantness factor was composed of three items, i.e., pain unpleasantness experienced at the three pain intensity levels in the previous week. The pain suffering factor was composed of negative emotions (depression, anxiety, frustration, anger, and fear) and negative beliefs (pain interference, ability to endure pain, ability to control pain, and belief that pain will be cured). The pain behaviors factor was composed of five factors: pain behavior at home, social reinforcement of pain behavior, family or home related responsibilities, pain contingent down time, and observed pain behaviors.

Table 4.31 shows that factor loadings estimated for the original stages of pain model in the current study were comparable to those estimated in a previous confirmatory factor analysis.[310] The measurement and structural components of the stages of pain model can be viewed in Figure 4.2. The chi-square value for the original stages of pain model was 349.6 with 167 degrees of freedom ($p < 0.001$). The goodness of fit statistics (Table 4.32) suggested that the data do not fit the model adequately.

[310] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain*. 1996;68:157-167.

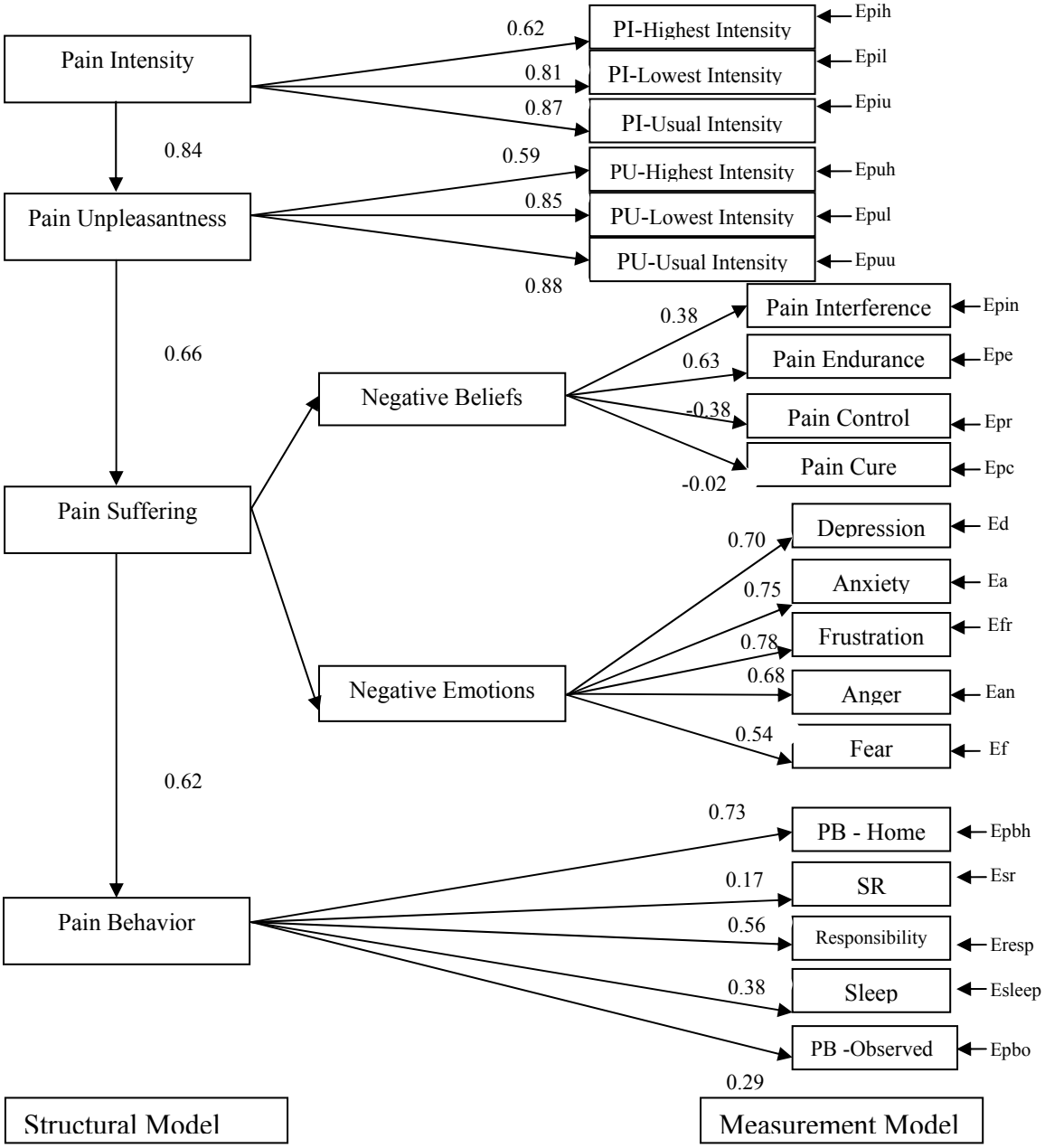
Three indicators were dropped from subsequent analysis, since weak factor loading estimates were observed: belief that pain will be cured (-0.02), social reinforcement for pain behavior (0.17), and observed pain behaviors (0.29).

Table 4.31 Comparison of Factor Loadings for Pain Intensity, Pain Unpleasantness, Pain Suffering, and Pain Behavior Constructs between Current Study and Wade et al. Study

Construct	**Indicator**	**Factor Loading**	
		Current Study	**Wade et al.[311] Study**
Pain Intensity (PI)	PI – Highest Level	0.62	0.45
	PI – Lowest Level	0.81	0.69
	PI – Usual Level	0.87	0.89
Pain Unpleasantness (PU)	PU – Highest Level	0.59	0.60
	PU – Lowest Level	0.85	0.64
	PU – Usual Level	0.88	0.95
Pain Suffering (PS)			
Negative Beliefs	Pain Interference	0.38	0.43
	Ability to Endure Pain	0.63	0.47
	Ability to Control Pain	-0.38	0.14
	Belief that Pain will be Cured	-0.02	0.15
Negative Emotions	Depression	0.70	0.78
	Anxiety	0.75	0.68
	Frustration	0.78	0.75
	Fear	0.54	0.57
	Anger	0.68	0.62
Pain Behaviors (PB)	Pain Behavior at Home	0.73	0.52
	Social Reinforcement of Pain Behavior	0.17	0.55
	Home and Family Related Responsibilities	0.56	0.49
	Pain Contingent Down Time	0.38	0.26
	Observed Pain Behaviors	0.29	0.35

[311] Ibid

Figure 4.2 Standardized Parameter Estimates of Original Baseline Stages of Pain Confirmatory Factor Model



PI-pain intensity, PU-pain unpleasantness, Pain Endurance – ability to endure pain, Pain control-ability to control pain, Pain Cure-belief that pain will be cured, PBHome-pain behavior at home, SR-social reinforcement of pain behavior, Responsibility-home and family responsibilities, sleep-pain contingent down time, pi/uh- pain intensity/unpleasantness at highest level, pi/ul-pain intensity/unpleasantness at

lowest level, pi/uu-pain intensity/unpleasantness at usual level, pin-pain interference, pe-pain endurance, pr-pain reduction, pc-pain cure, d-depression, a-anxiety, fr-frustration, an-anger, f-fear, pbh- pain behavior at home, resp-responsibility, sr-social reinforcement of pain, pbo- observed pain behavior.

Table 4.32 Goodness of Fit Statistics for the Stages of Pain Model

Variable	Chi square, df p – value	NFI	CFI	GFI	SRMR	RMSEA	90%CI RMSEA
Baseline Original Model	349.5, 167 p < 0.001	0.69	0.80	0.77	0.08	0.09	0.08, 0.10
Baseline Modification_1	32.4, 34 p = 0.54	0.92	1.00	0.95	0.05	0.00	0.00, 0.06
Baseline Modification_2	27.5, 33 p = 0.73	0.93	1.00	0.95	0.05	0.00	0.00, 0.04
Follow-up Modification_2	54.8, 33 p = 0.01	0.88	0.95	0.89	0.07	0.08	0.04, 0.12
Baseline Final Model	9.8, 12 P = 0.63	0.95	1.00	0.98	0.03	0.00	0.00, 0.07
Follow-up Final Model	19.5, 12 p = 0.10	0.91	0.96	0.94	0.07	0.07	0.00, 0.14

NFI – Bentler-Bonett Normed Fit Index
CFI – Comparitive Fit Index
GFI – Lisrel GFI Fit Index
SRMR – Standardized Root Mean Square Residual
RMSEA – Root Mean Square Error of Approximation
90%CI – 90 percent Confidence Interval

4.5.3 Baseline Stages of Pain Model - Modified

The next step in the analysis was to estimate a measurement model that was similar to the model which provided Wade and colleagues the best fit to their data. Wade's best fitting model excluded the following indicators from the original model: negative belief indicators, pain intensity and unpleasantness indicators at highest and lowest pain intensity levels, and the pain contingent down time indicator.

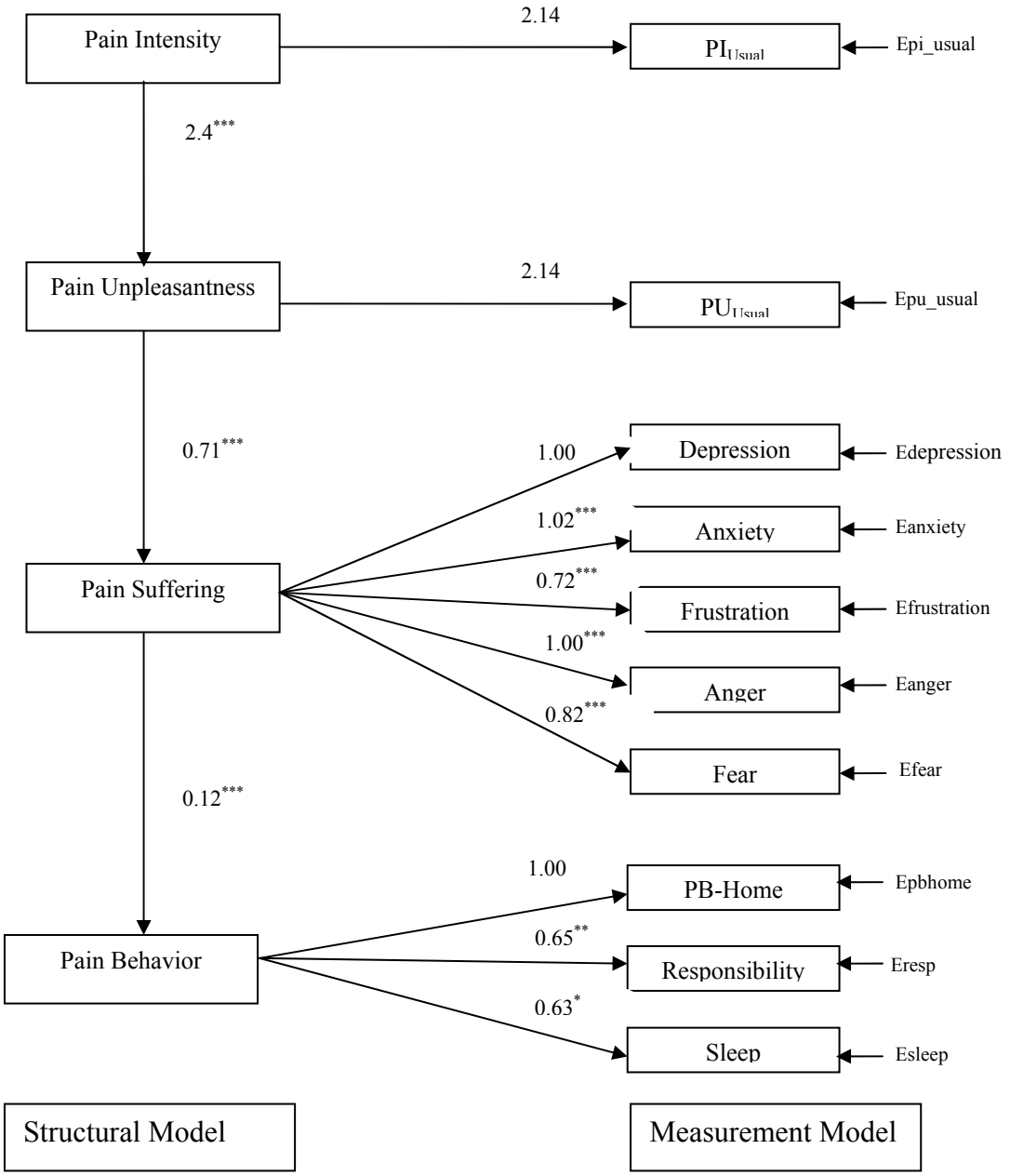
Thus, a model that closely resembled Wade's best fitting model was constructed. The modified model was referred to as the baseline stages of pain model – modification 1 (See Figure 4.3). This model included four factors: pain intensity, pain unpleasantness, pain suffering, and pain behaviors. The pain intensity factor was composed of a single indicator, i.e., pain intensity at the usual level. The pain unpleasantness factor was

composed of a single indicator, i.e., pain unpleasantness at the usual level. The pain suffering factor was composed of the negative emotions (depression, anxiety, frustration, anger, and fear). The pain behaviors construct was composed of three indicators, namely, pain behaviors at home, home and family related responsibilities, and pain contingent down time. The model evaluated with the current baseline data in this step was similar to Wade's best fitting model except for the indicators used to estimate the pain behavior factor. The previous best fitting model had excluded the "pain contingent down time" indicator, while including the observed pain behaviors and social reinforcement for pain behaviors indicators. The latter two indicators were dropped from this analysis due to non-significant factor loadings as described above.

In order to estimate any meaningful model, the degrees of freedom in the model being tested should be greater than the corresponding null model. Models containing factors with single indicators may be over-identified by fixing measurement error variance to zero or by providing reasonable start values or best guess estimates. Fixing error variance to zero assumes that the indicator has been measured perfectly. Since the pain intensity and pain unpleasantness factors were composed of single indicators, the measurement error variance estimates of each indicator generated in the previous run of the model were utilized as "best guess estimates" of measurement error variances for the average pain intensity and pain unpleasantness indicators in subsequent models.

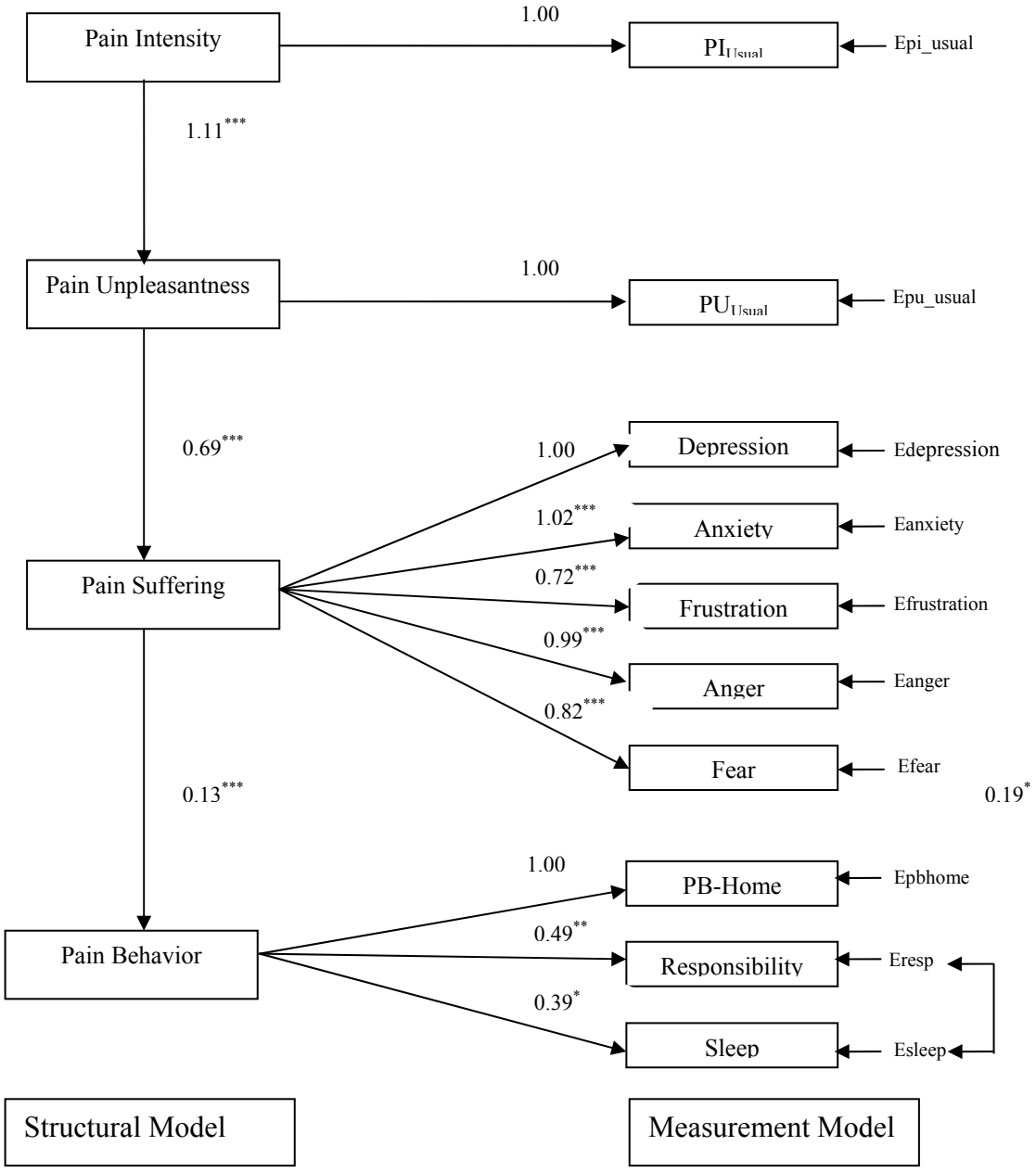
Model fit improved significantly for the baseline stages of pain model – modification 1 (chi-square = 32.4, df = 34, p = 0.54). The chi-square and goodness of fit statistics indicate that the model fits the data well (Table 4.30). Results from the modification indices suggested that the chi-square statistic would decrease further by freely estimating the covariance between measurement errors of the "pain contingent down time" and "home or family related responsibilities" indicators. The resulting modified model, which was referred to as baseline stages of pain model – modification 2 can be viewed in Figure 4.4. The results indicated a significant improvement in model fit (chi-square = 27.5, df = 33, p = 0.73). Goodness of fit statistics for this model are presented in Table 4.30.

Figure 4.3 Unstandardized Parameter Estimates of Baseline Stages of Pain Confirmatory Factor Model – Modification 1



PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behavior at home, Resp- Home or Family Related Responsibilities, Sleep – Pain Contingent Down Time
* - p<0.05, **-p<0.01, ***-p<0.001

Figure 4.4 Unstandardized Parameter Estimates of Baseline Stages of Pain Confirmatory Factor Model – Modification 2



PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behavior at home, Resp- Home or Family Related Responsibilities, Sleep – Pain Contingent Down Time
* - p<0.05, **-p<0.01, ***-p<0.001

4.5.4 Follow-up Stages of Pain Model – Modification 2

A model similar to the baseline stages of pain model – modification 2 was estimated with the follow-up data. The measurement and structural components of the follow-up stages of pain model – modification 2 can be viewed in Figure 4.5. The results from the follow-up data indicated that the model failed to fit the data adequately and should be rejected (chi square = 54.8, d.f. = 33, p = 0.01).

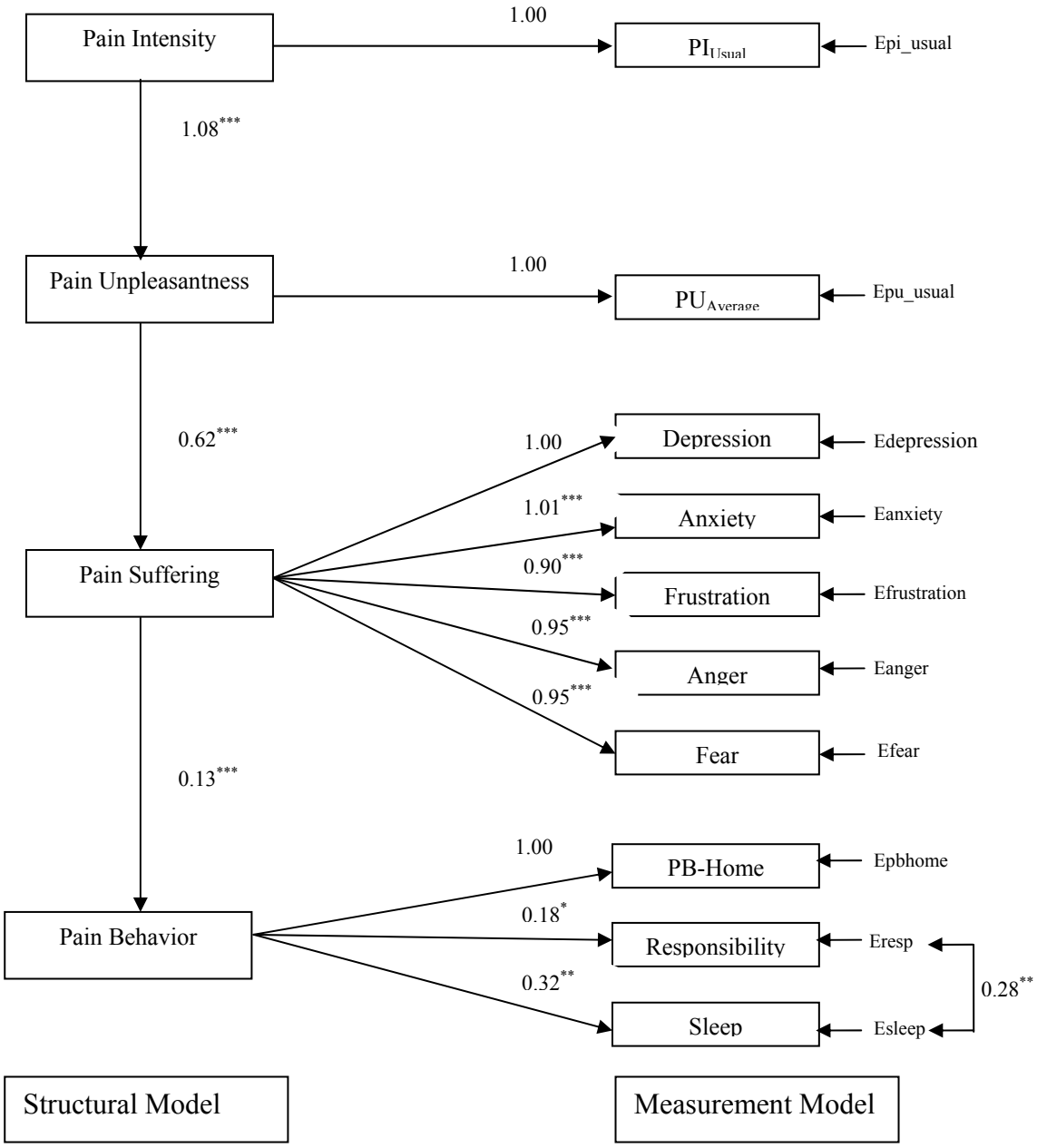
An examination of the residual covariance matrix showed that residual variances for three indicators of the pain suffering construct (frustration, anger, and fear) were negative. The magnitude of the negative variances for frustration, anger, and fear indicators were -0.62, -0.01, and -0.01 respectively. Negative residual variance is indicative of multicollinearity, which may contribute to model misspecification.[312] Additionally, these indicators would have contributed to estimation problems in subsequent models. Thus, these indicators were dropped from the follow-up and baseline models.

Removal of the offending indicators resulted in excellent model fit for both the baseline and follow-up models. The model without the three indicators will be referred to as the stages of pain model – final model. The measurement and structural components of the stages of pain – final model at baseline and follow-up can be viewed in Figures 4.6 and 4.7, respectively.

The chi-square fit test showed that the stages of pain - final model at baseline (chi-square = 9.8, df = 12, p = 0.63) and follow-up (chi-square = 19.5, df = 12, p = 0.10) fit the data adequately. Goodness of fit indices for these models can be viewed in Table 4.30.

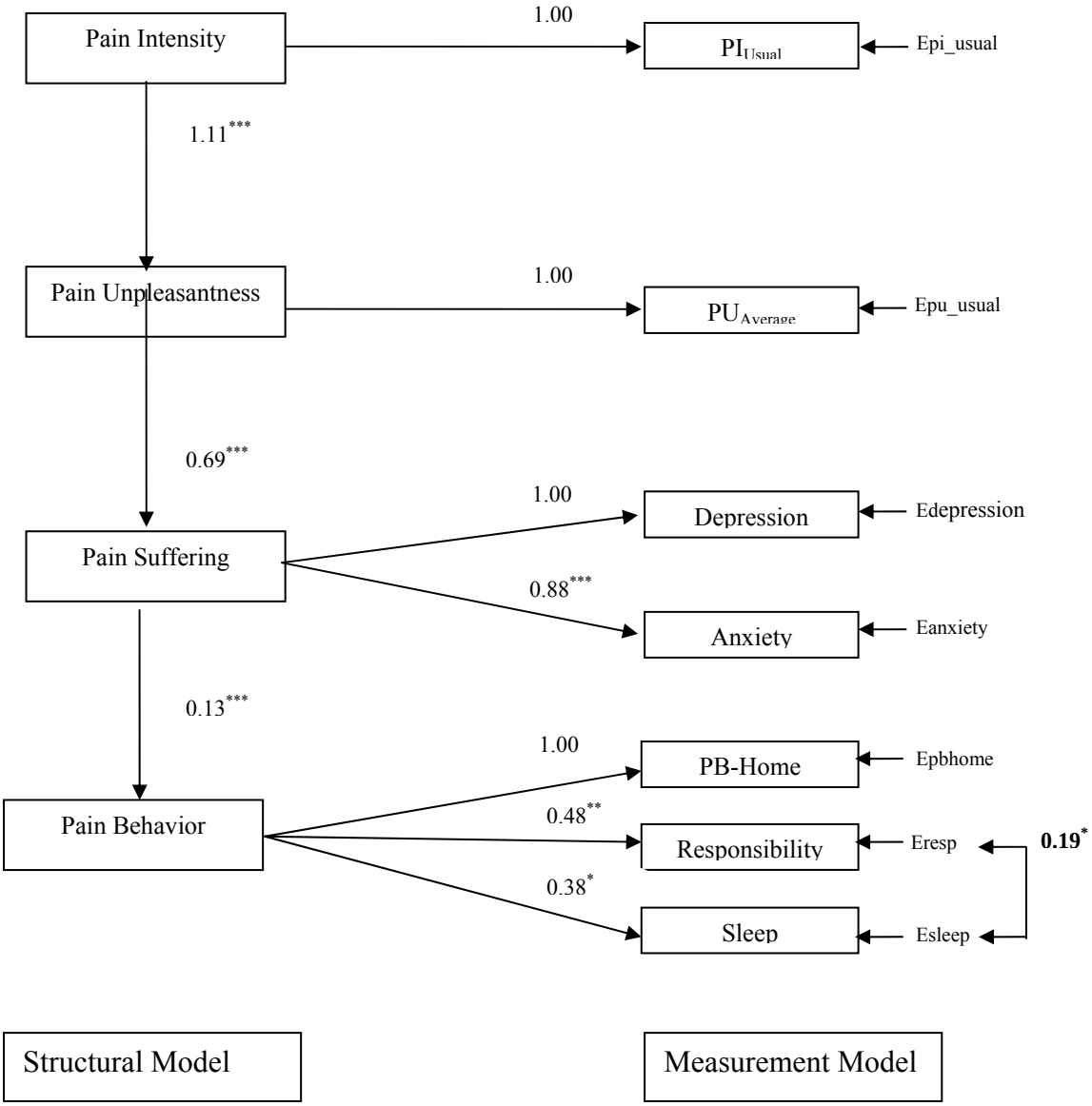
[312] Estimator conditioning diagnostics for covariance structure models. Sociological Methods and Research. 1994;23:200-229.

Figure 4.5 Unstandardized Parameter Estimates of Follow-up Stages of Pain Confirmatory Factor Model – Modification 2



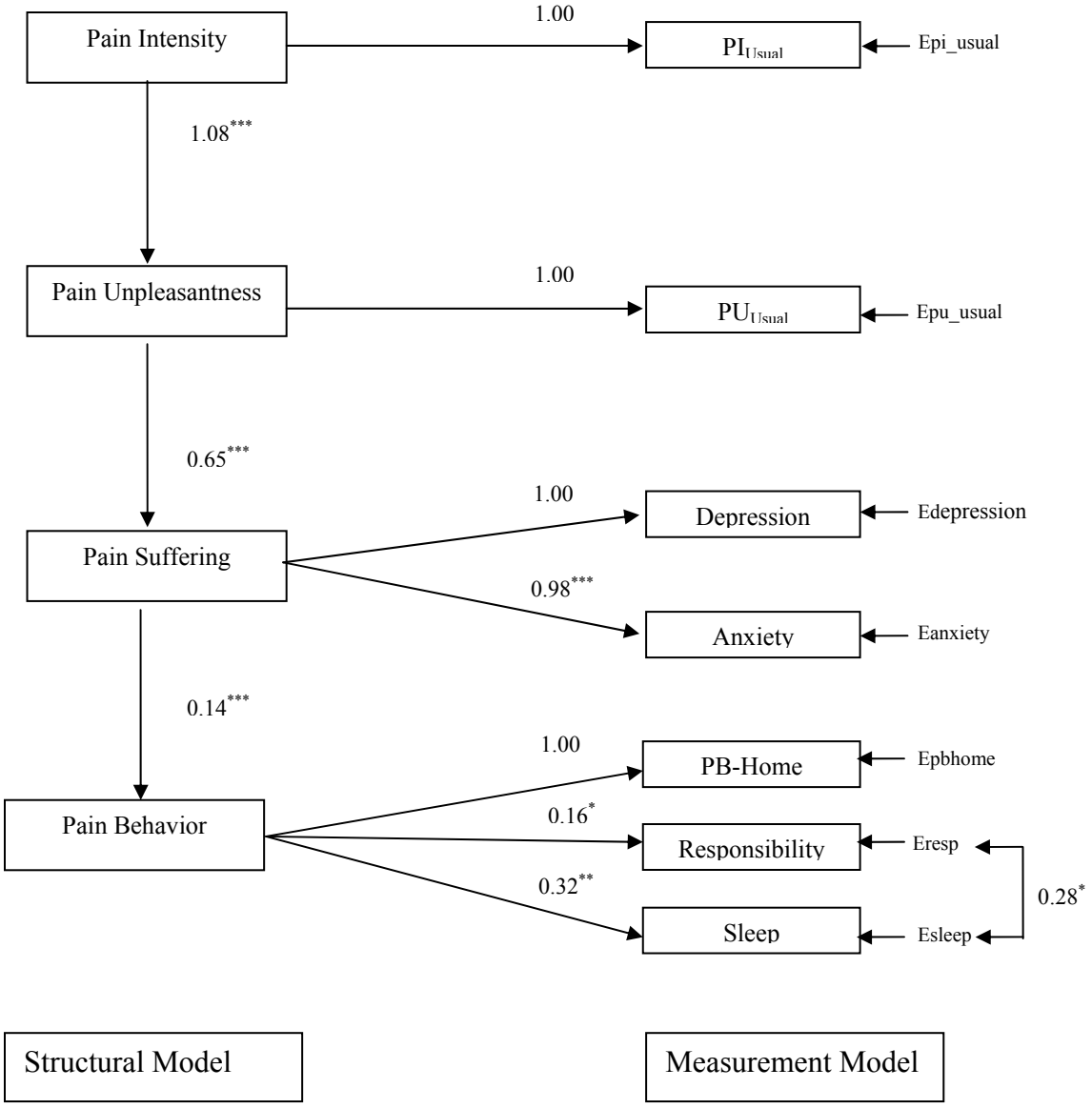
PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behaviors at home, Resp- Home or Family Related Responsibilities
* - p<0.05, **-p<0.01, ***-p<0.001

Figure 4.6 Unstandardized Parameter Estimates of Baseline Stages of Pain Confirmatory Factor Model – Final Model



PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behaviors at home, Resp- Home or Family Related Responsibilities
* - p<0.05, **-p<0.01, ***-p<0.001

Figure 4.7 Unstandardized Parameter Estimates of Follow-up Stages of Pain Confirmatory Factor Model – Final Model



PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behaviors at home, Resp- Home or Family Related Responsibilities
* - p<0.05, **-p<0.01, ***-p<0.001

In order to determine the stability of the stages of pain model –final model from baseline to follow-up, the two models were compared simultaneously with and without constraints (Table 4.33). In each step, additional constraints such as equal measurement weights, equal measurement intercepts, equal structural weights, equal structural intercepts, equal structural means, equal structural covariances, equal structural residuals, and equal measurement residuals were imposed on the two models simultaneously.

Simultaneous analysis of the baseline and follow-up final models showed that model fit to the data was adequate when factor loadings at baseline and follow-up were constrained to be equal (Table 4.33 – model with factor loadings constrained to be equal). The results suggested that the constructs being measured at baseline and follow-up are reliable. The baseline and follow-up stages of pain model can be described as having partial measurement invariance.[313]

[313] Byrne BM, Shavelson RJ, Muthen B. Testing for the equivalence of factor covariance and mean structures: The issue of partial measurement invariance. *Psychological Bulletin*. 1989;105:456-466.

Table 4.33 Results of the Simultaneous Comparison of Baseline and Follow-up Stages of Pain – Final Models				
Model (Type of Constraint)	**Chi-square**	**DF**	**P**	**Chi-square/DF**
Unconstrained	32.272	24	.120	1.345
Model 1[a]	34.510	27	.152	1.278
Model 2[b]	67.801	34	.001	1.994
Model 3[c]	68.483	37	.001	1.851
Model 4[d]	68.483	37	.001	1.851
Model 5[e]	68.483	37	.001	1.851
Model 6[f]	73.737	38	.000	1.940
Model 7[g]	73.737	38	.000	1.940
Model 8[h]	73.737	38	.000	1.940
Saturated model	.000	0		
Independence model	396.297	42	.000	9.436

[a]Factor loadings are constrained to be equal
[b]Factor loadings and measurement intercepts are constrained to be equal
[c]Factor loadings, measurement intercepts, and structural weights are constrained to be equal
[d]Factor loadings, measurement intercepts and structural weights and intercepts are constrained to be equal
[e] Factor loadings, measurement intercepts, structural weights and intercepts, and structural means are constrained to be equal
[f] Factor loadings, measurement intercepts, structural weights and intercepts, and structural means and covariances are constrained to be equal
[g]Factor loadings, measurement intercepts, structural weights and intercepts, and structural means and covariances, and structural residuals are constrained to be equal
[h]Factor loadings, measurement intercepts, structural weights and intercepts, and structural means and covariances, and structural and measurement residuals are constrained to be equal

4.6 Two-Wave Models

It was demonstrated above that indicators at baseline and follow-up were reliable measures of the latent constructs they were believed to represent. Thus, this section of the results chapter is concerned with the analysis of data collected at baseline and follow-up simultaneously. All two-wave models incorporated data from only patients who completed both baseline and follow-up assessments. Data collected for the same individuals over two or more time periods are often correlated. In order to analyze the

effects of an intervention, the effects of baseline variables on corresponding follow-up variables should be controlled.

Data collected over two waves may be modeled with synchronous and/or lagged effects.

Equation 4.1 represents a basic regression model:

$$Y_t = \beta_0 + \beta_1 X_t + \varepsilon_t \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots 4.1$$

$$Y_t = \beta_0 + \beta_1 X_t + \beta_2 Y_{t-1} + \varepsilon_t \quad \ldots\ldots\ldots\ldots\ldots 4.2$$

Y_t in equation 4.2 is assumed to be predicted from exogenous variable (X_t), the lagged dependent variable (Y_{t-1}) and a random error term with constant variance, with no autocorrelation and no correlation with any of the predictor terms in the equation.

Panel data represented in equation 4.2 model only the synchronous or co-temporal effect. An implicit assumption of the model is that the effect of X on Y is almost immediate. "It cannot be claimed that X causes Y instantaneously, but rather the causal lag for X to influence Y is short, relative to the time elapsed between waves of measurement."[314]

For situations in which there is a lag or delay between the effect of X on Y, and the interval between two measurements exceeds the delay, a lagged model may be more appropriate. In a lagged model, X_t would be replaced by X_{t-1} in equation 4.2. The identification of the lagged causal structure is a complex issue due to a general lack of knowledge about the time required by one variable to influence another and the relation of this lag to the time intervals in which data is measured. Therefore, Finkel suggests that specification of the lag structure should be influenced by theory first and data next. Models with both synchronous and lag effects may be estimated together. Such a model would be represented as:

$$Y_t = \beta_0 + \beta_1 X_t + \beta_2 Y_{t-1} + \beta_3 X_{t-1}\ \varepsilon_t \quad \ldots\ldots 4.3$$

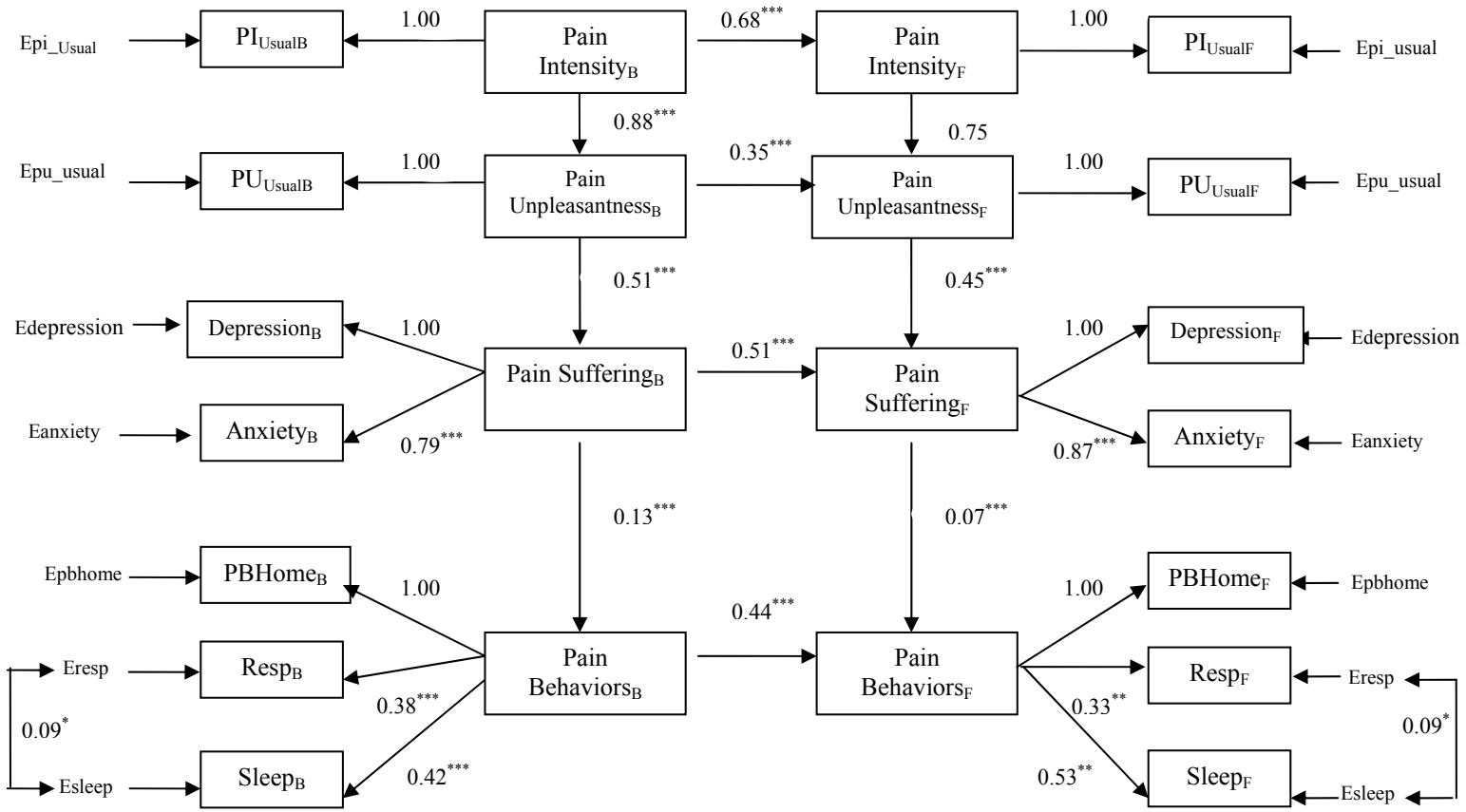
[314] Finkel SE. Causal analysis with panel data. Sage Publications. 1995. Thousand Oaks, CA. pp 12.

In the present study, long-acting morphine therapy was introduced at the time of baseline assessments as part of the therapeutic strategy. The objective of the study was to evaluate the effects of long-acting morphine therapy on pain and cognitive function at follow-up. In order to evaluate this objective, a synchronous effects model of the two-wave data seemed most appropriate.

4.6.1 Stages of Pain – Two Wave Model

The best fitting baseline and follow-up stages of pain models (final models) were combined to form a longitudinal (two-wave) model. As described above, only synchronous effects were analyzed in this model. Paths from each factor at baseline to the corresponding factor at follow-up were estimated. The covariance paths between measurement errors of the same indicator at baseline and follow-up were also estimated to account for autocorrelation. The resulting model is depicted in Figure 4.8. Although measurement error paths were estimated, they are not drawn in the figure due to space considerations. No additional constraints were imposed on this model. According to the exact chi-square fit test (chi square = 72.2, df = 65, p 0.25), the data fit the two-wave stages of pain model adequately.

Figure 4.8 Unstandardized Parameter Estimates of the Two-Wave Stages of Pain Confirmatory Factor Model – Final Model



PI-Pain Intensity, PU-Pain Unpleasantness, PB-Pain Behavior at home, Resp- Home or Family Related Responsibility, Sleep – Pain Contingent Down Time B-Baseline, F-Follow-up, E- Measurement Error. All corresponding E's across the two waves were correlated. * - $p<0.05$, **-$p<0.01$, ***-$p<0.001$

4.6.2 Hypothesized Study Model

The next step in the analysis was to determine fit of the hypothesized study model. A total of three tests, digit span test (DST), digit symbol test (DSYT), and paced auditory serial addition test (PASAT), which assess cognitive function were administered to patients. Thus, three models, each evaluating the associations between a test of cognitive function and various exogenous and endogenous variables, were constructed.

Except for the dependent variables, all three models (DST, DSYT, and DSYT) included common factors. Each model included the following factors:

- Age
    - This factor was formed with a single indicator, i.e. reported age. In order to estimate a factor with a single indicator, the error variance associated with a single indicator may be estimated or assumed to be zero. Age was assumed to have been measured perfectly, and thus, the error variance associated with this indicator was fixed to zero.
- Gender
    - Gender was reported in a dichotomous fashion, i.e., male or female. This factor was composed of a single indicator. Gender was assumed to have been measured perfectly, and thus, the error variance associated with this indicator was fixed to zero.
- Ethnicity/Race
    - Patients reported their ethnicity during the interview. A majority of the respondents (n = 53, 61%) were Caucasian. For the SEM analysis, this variable was dichotomized to represent two groups, i.e., Caucasians and others. The reported ethnicity indicator used to form this construct was assumed to have been measured perfectly. Thus, the error variance associated with this indicator was fixed to zero.
- Stages of pain model factors – Final Model:
    - The stages of pain final model included the following constructs at baseline and follow-up: pain intensity, pain unpleasantness, pain suffering

and pain behaviors. The measurement and structural portions of the SOPM were described above.

- Valium equivalent dose (VED)
  - VED was calculated by converting patient-reported average daily benzodiazepine dose into standard valium equivalent units. Thus, an average daily valium equivalent dose was calculated. A natural log transformation was applied to this variable. The purpose of the transformation was to minimize the magnitude of difference in the variance of modeled variables as described in Section 4.1.3 (See Table 4.2). Thus, the natural log transformations of the VED (lnVED) served as the indicator for the VED factor. Measurement error variance associated with the lnVED indicator was calculated using the formula:

$$\text{Measurement Error variance} = (1 - \text{reliability}) * \text{Variance} \quad \text{....} \quad 4.4$$

Based on the values in Table 4.34, measurement error variance associated with lnVED was estimated to be 0.17.

- Morphine Equivalent Dose at baseline (MED_B) and follow-up (MED_F)
  - MED_B and MED_F were calculated by converting the average daily narcotic analgesic doses at baseline and follow-up into morphine equivalent units. As described in the data screening procedures, large skewness and kurtosis values were observed for MED_B and MED_F, which suggested that these variables did not follow a normal distribution. Therefore, natural log transformations were applied to MED_B and MED_F values. These transformed values, i.e., $lnMED_B$ and $lnMED_F$ served as single indicators for MED_B and MED_F factors. Measurement error variance for $lnMED_B$ (0.15) and $lnMED_F$ (0.10) was estimated by substituting values from Table 4.34 in equation 4.3.

The formation of the dependent variable factors will be discussed separately, along with the results for each model.

Table 4.34 Measurement Error Variance Estimates of Single Indicators Utilized in the Hypothesized Models			
Variable	Variance	Test- Re-test Reliability (Cronbach's α)	Measurement Error[a]
lnMED Baseline Follow-up	 0.44 0.28	 0.65 0.65	 0.150 0.100
lnVED	1.7	0.9*	0.170
lnDST Baseline Follow-up	 0.08 0.07	 0.87 0.87	 0.010 0.009

* Although lnVED was a constant from baseline to follow-up, random error was assumed to be 0.1
a Measurement Error variance = (1 – reliability) * Variance

In order to estimate models with single indicators, the error variance associated with a single indicator may be assumed to take a value of zero. Alternatively, the error variance for single indicatory may be estimated. The factor loadings for each of the exogenous single indicators (age, gender, ethinicity/race) were fixed to one (1) and the error variance estimate was assumed to be zero. The exogenous factors were assumed to have been measured perfectly.

An alternate conceptualization of latent constructs of single indicators involves estimating the measurement error associated with these indicators. Estimates of reliability may be generated from the literature or the sample data. Measurement error variance of a single indicator used to form a latent factor was estimated with the following formula:[315,316]

Measurement Error variance = (1 – reliability) * Variance

[315] Hayduk L. Structural Equation Modeling with LISREL: Essentials and Advances(pages 119-122). 1987 Johns Hopkins University Press.
[316] Hayduk L. LISREL Issues Debates and Strategies (pages25-30). 1996, Hopkins University Press.

4.6.2.1 Autocorrelated Errors

This section continues to address the measurement component of the two-wave study model.

Since data for all variables except age, gender, ethnicity, and VED varied from baseline to follow-up, measurement error terms of corresponding indicators at baseline and follow-up were assumed to be autocorrelated. Thus covariance paths between each indicator at baseline and follow-up were freely estimated.

However, lnMEDB and lnMEDF were not assumed to be autocorrelated. The measure at baseline was composed of total morphine equivalent dose of short-acting narcotic analgesic. The measure at follow-up was the sum of Avinza dose and short-acting narcotic morphine equivalent dose used for breakthrough pain at follow-up. The error estimate between baseline and follow-up MED doses were not assumed to be autocorrelated for the following reasons:

- All patients were started on the lowest Avinza dose available (30mg/day), regardless of short-acting narcotic dose. Exceptions were made only in instances where patients were on exceedingly large doses of short-acting narcotic medications.
- Patient response to Avinza and the need for breakthrough narcotic dose was variable.
- The baseline dose was composed of only the short acting narcotic, while the follow-up dose comprised of the Avinza and breakthrough medication dose.

4.6.3 Hypothesized Digit Span Test (DST) Model

The dependent variable for the DST model was the digit span test factor at baseline (DST_B) and follow-up (DST_F). The DST_B factor was composed of two indicators, namely, digits span forward test and digits span backward test at baseline. The DST_F factor was composed of two indicators, i.e., digits span forward test and digits span backward test at follow-up. The structural component of the DST model can be viewed in Figure 4.9. Structural equation modeling results (chi square = 183.96, df = 212, p = 0.91) showed that the data were an excellent fit to the model. Goodness of fit indices for the model can be viewed in Table 4.35.

Table 4.35 Goodness of Fit Indices for the Hypothesized DST, DSYT, and PASAT Models

Variable	Chi sq, df p	NFI	CFI	SRMR	RMSEA	90%CI RMSEA
Two-wave Digit Span Model	183.9, 212 0.91	0.82	1.00	0.08	0.00	0.00, 0.01
Two-wave Digit Symbol Model	189.8, 174 0.19	0.80	0.97	0.09	0.03	0.00, 0.06
Two-wave PASAT Model –	204.2, 212 0.65	0.82	1.00	0.08	0.00	0.00, 0.03

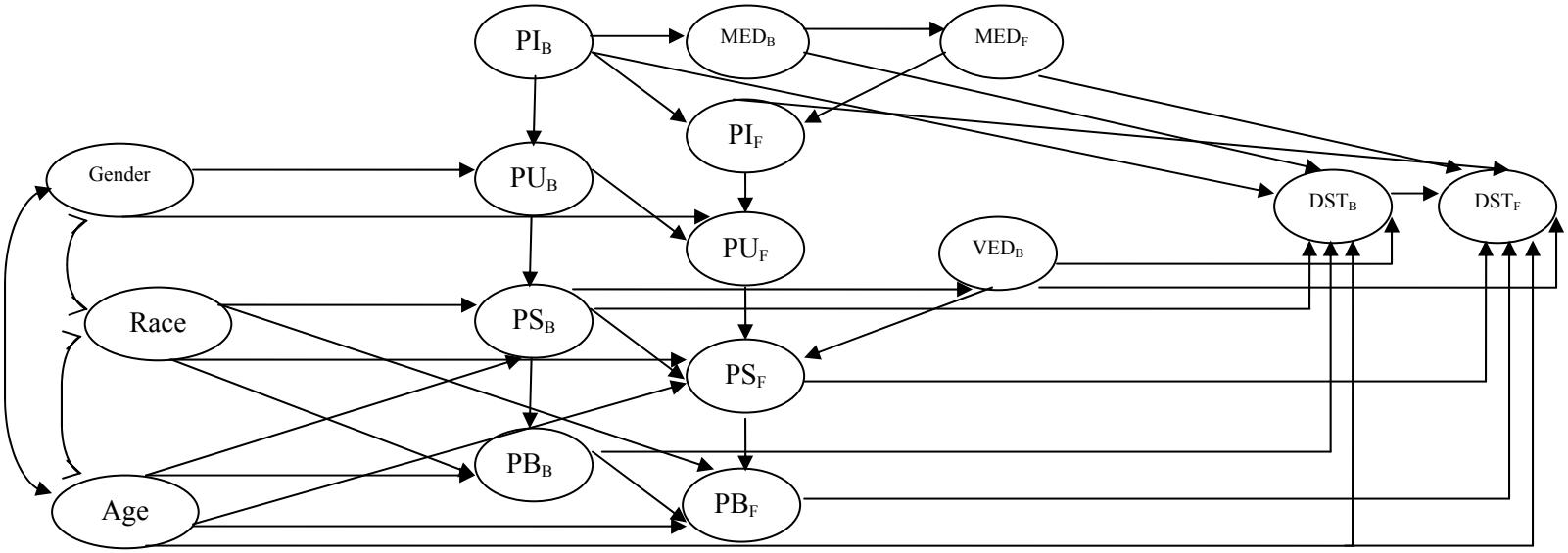
NFI- Normed Fit Index
CFI – Comparitive Fit Index
SRMR – Standardized Root Mean Square Residual
RMSEA – Root Mean Square Error of Approximation
90%CI – 90% Confidence Interval

Unstandardized parameter estimates of modeled associations are presented in Table 4.36.

Table 4.36 Table of Unstandardized Model Equations and Squared Multiple Correlations for the Hypothesized Digit Span Model	
Model Equations	R^2
$PU_B = 0.28G + 1.21^{***}PI + 2.45^{**}D_{PUB}$	0.69
$PU_F = -0.02G + 0.94^{***}PI_F + 0.28^{*}PU_B + 1.53^{*}D_{PUF}$	0.84
$PS_B = 0.01A - 2.07^{**}E + 0.60^{***}PU_B + 9.55^{***}D_{PSB}$	0.29
$PS_F = -0.01A - 0.90E + 0.47^{***}PU_F + 0.36VED + 0.46^{***}PS_B + 4.77^{***}D_{PSF}$	0.61
$PB_B = 0.02^{*}A + 0.03E + 0.14^{***}PS_B + 0.55^{***}D_{PBB}$	0.36
$PB_F = 0.00A + 0.03E + 0.09^{**}PS_F + 0.39^{**}PB_B + 0.39^{***}D_{PBF}$	0.47
$VED = 0.05PS_B + 1.56^{**}D_{VED}$	0.02
$MED_B = 0.04PI_B + 0.27^{***}D_{MEDB}$	0.03
$MED_F = 0.64^{***}MED_B + 0.07^{*}D_{MEDF}$	0.63
$PI_F = 0.70^{***}PI_B + 6.38^{*}MED_F - 4.97^{*}MED_B + 2.35D_{PIF}$	0.66
$DST_B = -0.03\text{^^}A - 0.05PS_B - 0.39^{*}PB_B + 0.68\text{^}MED_B - 0.01VED - 0.06PI_B + 1.00D^{*}_{DSTB}$	0.34
$DST_F = -0.02PS_F + 0.28PB_F - 0.38MED_F - 0.05VED + 0.02PI_F + 1.55^{***}DST_B + 0.40D_{DSTF}$	0.88

A – Age, G – Gender, E – Ethnicity/Race, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, DST-Digit Span Test, B-Baseline, F-Follow-up, D - Disturbance term associated with the latent variable
***p < 0.001, **p<0.01, *p<0.05 ^p = 0.08 ^^ p = 0.06

Figure 4.9 Hypothesized Two-Wave Digit Span Test Structural Model



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, DST – Digit Span Test Factor, B-Baseline, F-Follow-up

4.6.3.1 Hypothesis Testing – Digit Span Model

In this section, associations between age, stages of pain model factors, MED, VED, and Digit Span Test (DST) as the dependent variable are presented. The proposed hypothesis and corresponding results are listed in order. All parameter estimates are expressed as unstandardized units unless specified otherwise.

Table 4.37 presents a summary of the relationships examined in this section.

Table 4.37 Summary of Hypothesized Relationships for the Digit Span Model

Model Component	Regression Weight	Significance Level	Hypothesis	Hypothesis Supported
$MED_B \rightarrow DST_B$	0.68	0.08	H_{o1}	Yes
$VED \rightarrow DST_B$	-0.01	0.91	H_2	No
$PI_B \rightarrow DST_B$	-0.06	0.61	H_{o3}	Yes
$PS_B \rightarrow DST_B$	-0.05	0.46	H_4	No
$PB_B \rightarrow DST_B$	-0.39	0.05	H_5	Yes
$A \rightarrow PS_B$	0.01	0.83	H_6	No
$G \rightarrow PU_B$	-0.28	0.60	H_{o7}	Yes
$E \rightarrow PS_B$	-2.07	0.01	H_{o8}	No
$E \rightarrow PB_B$	0.03	0.84	H_{o9}	Yes
$A \rightarrow PB_B$	0.02	0.06	H_{o10}	Yes
$PI_B \rightarrow MED_B$	0.04	0.21	H_{11}	No
$PS_B \rightarrow VED$	0.05	0.20	H_{12}	No
$A \rightarrow DSYT_B$	-0.03	0.06	H_{13}	No
$MED_F \rightarrow DST_F$	-0.38	0.53	H_{o14}	Yes
$VED \rightarrow DST_F$	-0.05	0.70	H_{15}	No
$PI_F \rightarrow DST_F$	0.02	0.78	H_{o16}	Yes
$PS_F \rightarrow DST_F$	-0.02	0.70	H_{17}	No
$PB_F \rightarrow DST_F$	0.28	0.29	H_{18}	No
$A \rightarrow PS_F$	-0.01	0.72	H_{19}	No
$G \rightarrow PU_F$	-0.02	0.95	H_{o20}	Yes
$E \rightarrow PS_F$	-0.90	0.21	H_{o21}	Yes
$E \rightarrow PB_F$	0.03	0.84	H_{o22}	Yes
$A \rightarrow PB_F$	0.00	0.31	H_{o23}	Yes
$MED_F \rightarrow PI_F$	6.38	0.04	H_{24}	Yes
$VED \rightarrow PS_F$	0.36	0.17	H_{25}	No
$A \rightarrow DSYT_B$	0.02	0.33	H_{26}	No

A – Age, G – Gender, E – Ethnicity/Race, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, DST-Digit Span Test, B-Baseline, F-Follow-up

- H_{o1}: There is no association between morphine equivalent dose (MED) of short-acting narcotic analgesic agents and digit span test scores at baseline.

Results from the two-wave digit span model showed that there was a positive but insignificant association between MED and digit span test scores at baseline ($MED_B \rightarrow DST_B = 0.68$, SE = 0.40, p = 0.08). Since a log transformation was applied to the MED_B indicator, the coefficient implies that a one percent change in MED_B is associated with a 0.0068 unit change in DST scores.

The hypothesis was supported

- H_2: There is a linear and inverse relationship between benzodiazepine dose and digit span test scores at baseline.

  Results from the two-wave digit span model showed that there was no statistical association between valium equivalent dose of benzodiazepines taken by patients and digit span test scores at baseline ($VED \rightarrow DST_B = -0.01$, SE = 0.12, p = 0.91). Since a log transformation was applied to the VED indicator, the coefficient implies that a one percent change in VED is associated with a – 0.0001 unit change in DST scores.

  The hypothesis was not supported.

- H_{o3}: There is no direct association between pain intensity and digit span scores at baseline.

  Results from the two-wave digit span model showed that statistically, there was no direct effect of pain intensity on the digit span test scores at baseline ($PI_B \rightarrow DST_B = -0.06$, SE = 0.13, p = 0.61).

  The hypothesis was supported.

- H_4: There is a linear and inverse association between pain suffering and digit span subtest scores at follow-up.

  Results from the two-wave digit span model showed that there was no statistical association between pain suffering and digit span test scores at baseline ($PS_B \rightarrow DST_B = -0.05$, SE = 0.07, p = 0.46).

  The hypothesis was not supported.

- H_5: There is a linear and inverse association between frequency of pain behaviors and digit span subtest scores at baseline.

Results from the two-wave digit span model showed that there was a linear and inverse association between frequency of pain behaviors and digit span test scores at baseline (PB_B→ Digit Span = -0.39, SE = 0.20, p = 0.05).

The hypothesis was supported.

- H_6: There is a linear and inverse association between age and pain suffering.

  Results from the two-wave digit span model showed that there was no statistical association between pain suffering and age at baseline (Age → PS_B = 0.01, SE = 0.04, p = 0.83).

  The hypothesis was not supported.

- H_{o7}: There is no difference in baseline pain unpleasantness ratings between males and females.

  Results from the two-wave digit span model showed that there was no statistical difference in pain unpleasantness ratings between males and females (Gender → PU_B = -0.28, SE = 0.53, p = 0.60).

  The hypothesis was supported.

- H_{o8}: There is no significant association between ethnicity and pain suffering at baseline.

  Results from the two wave model with the DST as the dependent variable showed that Caucasians provided significantly lower pain suffering ratings than patients belonging to other ethnic groups at baseline. (Ethnicity → PS_B = -2.07, SE = 0.88, p < 0.01).

- H_{o9}: There is no significant association between ethnicity and pain behavior at baseline.

  Results from the two wave model with the DST as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at baseline. (Ethnicity → PB_B = 0.03, SE = 0.20, p = 0.84).

  The hypothesis was supported.

- H_{o10}: There is no significant association between age and pain behavior at baseline.

  Results from the two-wave model with the DST as the dependent variable showed that the association between pain behavior and age at baseline approached statistical significance (Age → PB_B = 0.02, SE = 0.01, p = 0.06).

  The hypothesis was supported.

- H_{11}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.

  Results from the two-wave DST model showed that there was no statistical association between pain intensity and MED at baseline (PI_B→ MED_B = 0.04, SE = 0.03, p = 0.21). Since a natural log transformation was applied to the MED indicator, the regression coefficient implies that a unit change in PI is associated with a four percent change in MED.

  The hypothesis was not supported.

- H_{12}: There is linear and direct association between pain suffering and valium equivalent dose at baseline

  Results from the two-wave DST model showed that there was no statistical association between pain suffering and VED at baseline (PS_B→ VED_B = 0.05, SE = 0.04, p = 0.20). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a unit change in PS is associated with a five percent change in VED.

  The hypothesis was not supported.

- H_{13}: There is an inverse association between age and DST at follow-up.

  Results from the two-wave DST model showed that association between age and DST at baseline approached statistical significance (Age → DST_B = -0.03, SE = 0.01, p = 0.06).

  The hypothesis was not supported.

- H_{o14}: There is no association between morphine equivalent dose (MED) of Avinza® plus breakthrough medication dose and digit span test scores at follow-up.

  Results from the two-wave digit span model showed that there is no association between the latent factor composed of natural log of Avinza® dose and morphine equivalent dose of short-acting narcotic breakthrough pain medication and digit span test scores at follow-up ($MED_F \rightarrow DST_F$ = - 0.38, SE = 0.61, p = 0. 53). Since a log transformation was applied to the MED_F indicator, the coefficient implies that a one percent change in MED_F is associated with a -0.0038 unit change in DST scores. MED_F and DST_F scores were controlled by their corresponding scores at baseline.

  The hypothesis was supported.

- H_{15}: There is a linear and inverse relationship between benzodiazepine dose and digit span subtest scores at follow-up.

  Results from the two-wave digit span model showed that there was no association between theVED and digit span test scores at follow-up ($VED_F \rightarrow DST_F$ = -0.05, SE = 0.14, p = 0.70). Since a log transformation was applied to the VED indicator, the coefficient implies that a one percent change in VED is associated with a -0.0005 unit change in DST scores. Digit span test score at follow-up was controlled by its corresponding score at baseline.

  The hypothesis was not supported.

- H_{o16}: There is no direct association between pain intensity and digit span subtest scores at follow-up.

  Results from the two-wave digit span model showed that there is no association between PI and digit span test scores at follow-up ($PI_F \rightarrow DST_F$ = 0.02 SE = 0.09, and p = 0.78). Pain intensity and DST at follow-up were controlled by their corresponding scores at baseline.

  The hypothesis was supported.

- H_{17}: There is a linear and inverse association between pain suffering and digit span subtest scores at follow-up.

  Results from the two-wave digit span model showed that there is no statistical relationship between pain suffering and digit span test scores at follow-up, controlling for pain suffering and digit span test scores at baseline. ($PS_F \rightarrow DST_F$ = -0.02 SE = 0.07, and p = 0.70).

  The hypothesis was not supported.

- H_{18}: There is a linear and inverse association between frequency of pain behaviors and digit span subtest scores.

  Results from the two-wave digit span model showed that there is no statistical relationship between frequency of pain behaviors and digit span test scores at follow-up, controlling for pain behaviors and digit span test scores at baseline. ($PB_F \rightarrow DST_F$ = 0.28 SE = 0.26, and p = 0.29).

  The hypothesis was not supported.

- H_{19}: There is a linear and inverse association between age and pain suffering at follow-up.

  Results from the two-wave digit span model showed that there was no statistical association between pain suffering and age at follow-up (Age $\rightarrow$ PS_F = - 0.01, SE = 0.03, p = 0.72).

  The hypothesis was not supported.

- H_{o20}: There is no difference in follow-up pain unpleasantness ratings between males and females.

  Results from the two-wave digit span model showed that there was no statistical difference in pain unpleasantness ratings between males and females (Gender $\rightarrow$ PU_F = - 0.02, SE = 0.43, p = 0.95).

  The hypothesis was supported.

- H_{o21}: There is no significant association between race and pain suffering at follow-up.

Results from the two wave model with the DST as the dependent variable showed no significant difference in pain suffering ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PS_F = -0.90, SE = 0.71, p < 0.21).

The hypothesis was supported.

- H_{o22}: There is no significant association between race and pain behavior at follow-up.

  Results from the two wave model with the DST as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PB_F = 0.03, SE = 0.16, p = 0.84).

  The hypothesis was supported.

- H_{o23}: There is no significant association between age and pain suffering at follow-up.

  Results from the two-wave model with the DST as the dependent variable showed that there was no statistical association between pain behavior and age at follow-up (Age →PB_F= 0.00, SE = 0.00, p = 0.31).

  The hypothesis was supported.

- H_{24}: There is a linear and direct association between morphine equivalent dose and pain intensity at follow-up.

  Results from the two-wave DST model showed that there was a statistically significant direct association between pain intensity and MED at follow-up (MED_F → PI_F = 6.38, SE = 3.01, p = 0.04). Since a log transformation was applied to the MED_F indicator, the coefficient implies that a one percent change in MED_F is associated with a 0.06 unit change in pain intensity ratings.

- H_{25}: There is a linear and direct association between valium equivalent dose and pain suffering at follow-up.

  Results from the two-wave DST model showed that there was no statistical association between pain suffering and VED at follow-up

($VED_F \rightarrow PS_F = 0.36$, SE = 0.26, p = 0.17). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a one percent change in VED is associated with a 0.03 unit change in PS.

The hypothesis was not supported.

- H_{26}: There is an inverse association between age and DST at follow-up.

  Results from the two-wave DST model showed that there was no statistically significant association between age and DST at follow-up (Age $\rightarrow DST_F = 0.02$, SE = 0.02, p = 0.33).

  The hypothesis was not supported.

4.6.4 Hypothesized Digit Symbol Test (DSYT) Model

The dependent variable for the DSYT model was the digit symbol test factor at baseline ($DSYT_B$) and follow-up ($DSYT_F$). The $DSYT_B$ and $DSYT_F$ factors were each composed of a single indicator, i.e., digit symbol test score at baseline and follow-up. A natural log transformation was applied to the test scores. The purpose of the transformation was to minimize the magnitude of difference in the variance of modeled variables (Table 4.2 presents the observed variance for digit symbol test scores at baseline and follow-up). Thus, the natural log transformations of the DSYT scores at baseline ($lnDSYT_B$) and follow-up ($ln\ DSYT_F$) served as indicators for the $DSYT_B$ and $DSYT_F$ factors, respectively. Measurement error variance associated with the $lnDSYT_B$ (0.016) and $lnDSYT_F$ (0.014) indicators was estimated by substituting values from Table 4.34 in equation 4.3. The structural component of the DSYT model can be viewed in Figure 4.10. Structural equation modeling results (chi square = 189.85, df = 174, p = 0.19) showed that the data were an excellent fit to the model. Goodness of fit indices for the model can be viewed in Table 4.35.

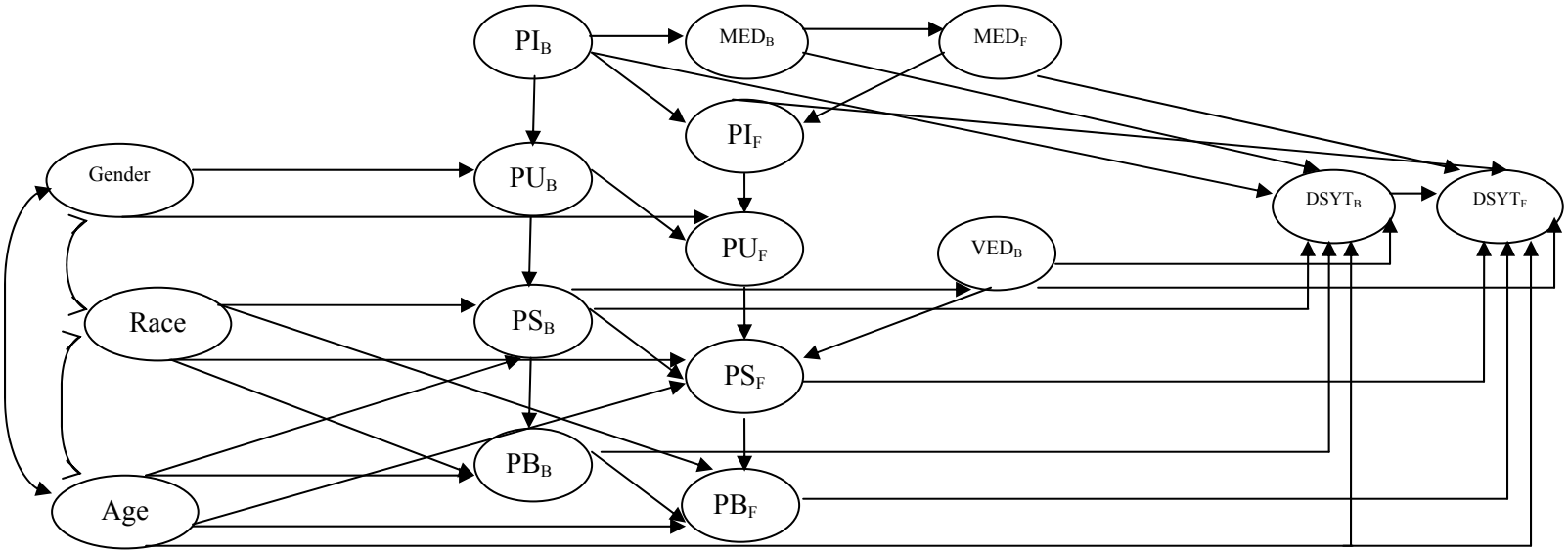
Unstandardized parameter estimates of modeled associations are presented in Table 4.38.

Table 4.38 Table of Unstandardized Model Equations and Squared Multiple Correlations for the Modified Digit Symbol Model

Model Equations	R^2
$PU_B = 0.31G + 1.20^{***}PI_B + 2.52^{**}D_{PUB}$	0.69
$PU_F = -0.04G + 0.93^{***}PI_F + 0.31^{*}PU_B + 1.39D_{PUF}$	0.86
$PS_B = 0.01A - 1.32^{*}E + 0.32^{**}PU_B + 5.77^{**}D_{PSB}$	0.18
$PS_F = -0.01A - 0.85E + 0.41^{***}PU_F + 0.51^{***}PS_B + 0.35VED + 3.38^{***}D_{PSF}$	0.60
$PB_B = 0.007A - 0.02E + 0.06^{**}PS_B + 0.09^{*}D_{PBB}$	0.29
$PB_F = -0.007^{*}A - 0.02E \quad 0.03^{*}PS_F + 0.40^{**}PB_B + 0.01D_{PBF}$	0.76
$VED = 0.04PS_B + 1.58^{***}D_{VED}$	0.01
$MED_B = 0.04PI_B + 0.27^{***}D_{MEDB}$	0.03
$MED_F = 0.61^{***}MED_B + 0.07^{*}D_{MEDF}$	0.58
$PI_F = 0.68^{***}PI_B + 5.77^{*}MED_F - 4.38MED_B + 2.46^{*}D_{PIF}$	0.61
$DSYT_B = -0.007^{*}A + 0.002PS_B - 0.13PB_B + 0.07MED_B - 0.05^{*}VED - 0.007PI_B + 0.05^{***}D_{DSYTB}$	0.21
$DSYT_F = 0.003PS_F - 0.03PB_F - 0.008MED_F + 0.012VED - 0.00PI_F + 0.87^{***}DSYT_B + 0.01^{*}D_{DSYTB}$	0.83

A – Age, G – Gender, E – Ethnicity/Race, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, DSYT-Digit Symbol Test, B-Baseline, F-Follow-up, D - Disturbance term associated with the latent variable
***p < 0.001, **p<0.01, *p<0.05

Figure 4.10 Hypothesized Two-Wave Digit Symbol Test Measurement Model



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, DSYT – Digit SymbolTest Factor, B-Baseline, F-Follow-up

4.6.4.1 Hypothesis Testing – Digit Symbol Model

In this section, associations between age, stages of pain model factors, MED, VED, and Digit Symbol Test (DSYT) as the dependent variable are presented. The proposed hypothesis and corresponding results are listed in order. All parameter estimates are expressed as unstandardized units unless specified otherwise.

A summary of the examined relationships is presented in Table 4.39.

Table 4.39 Summary of Hypothesized Relationships for the Digit Symbol Model

Model Component	Regression Weight	Significance Level	Hypothesis	Hypothesis Supported
$MED_B \rightarrow DSYT_B$	0.075	0.23	H_{o27}	Yes
$VED \rightarrow DSYT_B$	-0.05	0.03	H_{28}	Yes
$PI_B \rightarrow DSYT_B$	-0.007	0.70	H_{o29}	Yes
$PS_B \rightarrow DSYT_B$	0.002	0.90	H_{30}	No
$PB_B \rightarrow DSYT_B$	-0.13	0.16	H_{31}	No
$A \rightarrow PS_B$	0.01	0.55	H_{32}	No
$G \rightarrow PU_B$	0.31	0.56	H_{o33}	Yes
$E \rightarrow PS_B$	-1.32	0.02	H_{o34}	No
$E \rightarrow PB_B$	-0.02	0.73	H_{o35}	Yes
$A \rightarrow PB_B$	0.007	0.10	H_{o36}	Yes
$PI_B \rightarrow MED_B$	0.04	0.23	H_{37}	No
$PS_B \rightarrow VED$	0.04	0.30	H_{38}	No
$A \rightarrow DSYT_B$	-0.007	0.03	H_{39}	Yes
$MED_F \rightarrow DSYT_F$	-0.008	0.85	H_{o40}	Yes
$VED \rightarrow DSYT_F$	0.012	0.33	H_{41}	No
$PI_F \rightarrow DSYT_F$	0.00	0.94	H_{o42}	Yes
$PS_F \rightarrow DSYT_F$	0.003	0.722	H_{43}	No
$PB_F \rightarrow DSYT_F$	-0.03	0.75	H_{44}	No
$A \rightarrow PS_F$	-0.01	0.60	H_{45}	No
$G \rightarrow PU_F$	-0.04	0.92	H_{o46}	Yes
$E \rightarrow PS_F$	-0.85	0.11	H_{o47}	Yes
$E \rightarrow PB_F$	-0.02	0.64	H_{o48}	Yes
$A \rightarrow PB_F$	0.003	0.40	H_{o49}	Yes
$MED_F \rightarrow PI_F$	5.72	0.02	H_{50}	Yes
$VED \rightarrow PS_F$	0.35	0.09	H_{51}	No
$A \rightarrow DSYT_B$	-0.003	0.15	H_{52}	No

* This relationship may be considered significant.
- The hypothesis was not testable
A- Age, G – Gender, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, DSYT-Digit Symbol Test, B-Baseline, F-Follow-up

- H_{o27}: There is no association between morphine equivalent dose (MED) of short-acting narcotic analgesic agents and digit symbol test scores at baseline.

Results from the two wave model with the digit symbol test as the dependent variable showed that there was a positive but insignificant association between MED and DSYT at baseline ($MED_B \rightarrow DSYT_B$ = 0.075, SE = 0.06, p = 0.23). Since a log transformation was applied to indicators of both DSYT and MED at baseline, the coefficient implies that a one percent change in MED_B is associated with a 0.075 percent change in DSYT scores.

The hypothesis was supported.

- H_{28}: There is a linear and inverse relationship between benzodiazepine dose and digit symbol subtest scores.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was a significant inverse association between VED and $DSYT_B$ at baseline ($VED \rightarrow DSYT_B$ = -0.05, SE = 0.02, p = 0.03). Since a natural log transformation was applied to indicators of both DSYT and VED, the regression coefficient implies that a one percent change in VED is associated with 0.05 percent reduction in DSYT scores.

  The hypothesis was supported.

- H_{o29}: There is no direct association between pain intensity and digit symbol test scores at baseline.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was an insignificant association between pain intensity and digit symbol test at baseline ($PI_B \rightarrow DSYT_B$ = -0.007, SE = 0.01, p = 0.70). Since a natural log transformation was applied to the DSYT indicator, the regression coefficient implies that a unit change in PI is associated with a 0.7 percent reduction in digit symbol subtest scores.

  The hypothesis was supported.

- H_{30}: There is a linear and inverse association between pain suffering and digit symbol test scores at baseline

Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical association between pain suffering and digit symbol test at baseline ($PS_B \rightarrow DSYT_B$ = 0.002, SE = 0.01, p = 0.90). Since a natural log transformation was applied to the DSYT indicator, the regression coefficient implies that a unit change in PS is associated with a 0.2 percent increase in digit symbol subtest scores.

The hypothesis was not supported.

- H_{31}: There is a linear and inverse association between frequency of pain behaviors and digit symbol subtest scores.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was an inverse, but insignificant statistical association between frequency of pain behaviors and digit symbol test at baseline ($PB_B \rightarrow DSYT_B$ = -0.13, SE = 0.09, p = 0.16). Since a natural log transformation was applied to the DSYT indicator, the regression coefficient implies that a unit increase in pain behavior frequency is associated with a 13 percent reduction in digit symbol subtest scores.

  The results imply a large, practically important association between pain behaviors and digit symbol test scores; however, the hypothesis was not supported.

- H_{32}: There is a linear and inverse association between age and pain suffering at baseline.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical association between age and pain suffering at baseline (Age $\rightarrow PS_B$ = 0.01, SE = 0.03, p = 0.55)

  The hypothesis was not supported.

- H_{o33}: There is no difference in pain unpleasantness ratings between males and females at baseline.

Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical difference in pain unpleasantness ratings between males and females at baseline (Gender → $PU_B = 0.31$, SE = 0.53, p = 0.56)

The hypothesis was supported.

- H_{o33}: There is no association between ethnicity and pain suffering at baseline.

  Results from the two wave model with the DSYT as the dependent variable showed that Caucasians provided significantly lower pain suffering ratings than patients belonging to other ethnic groups at baseline. (Ethnicity → $PS_B = -1.32$, SE = 0.58, p = 0.02).

  The hypothesis was not supported.

- H_{o34}: There is no association between ethnicity and pain behavior at baseline.

  Results from the two wave model with the DSYT as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at baseline. (Ethnicity → $PB_B = -0.02$, SE = 0.07, p = 0.73).

  The hypothesis was supported.

- H_{o35}: There is no significant association between age and pain behavior at baseline.

  Results from the two-wave model with the DSYT as the dependent variable showed that there no statistical association between pain behavior and age at baseline (Age →$PB_B = 0.007$, SE = 0.004, p = 0.10).

  The hypothesis was supported.

- H_{36}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.

  Results from the two-wave DSYT model showed that there was no statistical association between pain intensity and MED at baseline (PI_B→ $MED_B = 0.04$, SE = 0.03, p = 0.23). Since a natural log transformation was applied to the MED indicator, the regression

coefficient implies that a unit change in PI is associated with a four percent change in MED.

The hypothesis was not supported.

- H_{37}: There is linear and direct association between pain suffering and valium equivalent dose at baseline.

  Results from the two-wave DSYT model showed that there was no statistical association between pain suffering and VED at baseline ($PS_B \rightarrow VED_B = 0.04$, SE = 0.05, $p = 0.30$). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a unit change in PS is associated with a four percent change in VED.

- H_{38}: There is an inverse association between age and DSYT at baseline.

  Results from the two-wave DSYT model showed that there was a statistically significant association between age and DSYT at baseline ($Age \rightarrow DSYT_B = -0.007$, SE = 0.01, $p < 0.05$). Since a log transformation was applied to the DSYT indicator, the regression coefficient implies that a one year increase in age is associated with a 0.7 percent reduction in DSYT.

  The hypothesis was supported.

- H_{o39}: There is no association between morphine equivalent dose (MED) of Avinza® plus breakthrough medication dose and digit symbol test scores at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was an insignificant association between MED and digit symbol test at follow-up ($MED_F \rightarrow DSYT_F = -0.008$, SE = 0.04, $p = 0.85$). Since natural log transformations were applied to indicators of both DSYT and MED at follow-up, the regression coefficient implies that a one percent change in MED is associated with a 0.008 percent reduction in DSYT scores at follow-up.

$DSYT_F$ and MED_F scores were controlled by their corresponding scores at baseline.

The hypothesis was supported.

- H_{40}: There is a linear and inverse relationship between benzodiazepine dose and digit symbol subtest scores at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical association between VED and digit symbol test at follow-up (VED → $DSYT_F$ = 0.012, SE = 0.01, p = 0.33). $DSYT_F$ score at follow-up was controlled by its corresponding scores at baseline. Since natural log transformations were applied to indicators of both DSYT and VED at follow-up, the regression coefficient implies that a one percent change in VED is associated with a 0.01 percent increase in DSYT scores at follow-up.

  The hypothesis was not supported.

- H_{o41}: There is no direct association between pain intensity and digit symbol subtest scores at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no association between pain intensity scores and digit symbol test at follow-up (PI_F → DSYT = 0.00 SE = 0.007, p = 0.94). $DSYT_F$ and PI_F scores at follow-up were controlled by their corresponding scores at baseline.

  The hypothesis was supported.

- H_{42}: There is a linear and inverse association between pain suffering and digit symbol subtest scores at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no significant association between pain suffering scores and digit symbol test at follow-up (PS_F → $DSYT_F$ = 0.003, SE = 0.008, p = 0.72). Since a log transformation was applied to the DSYT indicator, the regression coefficient implies that a

unit change in PS scores at follow-up was associated with a 0.3 percent increase in DSYT scores. $DSYT_F$ and PS_F scores were controlled by their corresponding scores at baseline.

The hypothesis was not supported.

- H_{43}: There is a linear and inverse association between frequency of pain behaviors and digit symbol subtest scores at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was a statistically insignificant inverse association between PB scores and digit symbol test at follow-up ($PB_F \rightarrow DSYT_F$ = -0.03, SE = 0.09, p = 0.675). Since a log transformation was applied to the DSYT indicator, the regression coefficient implies that a unit increase in pain behavior frequency at follow-up was associated with a 3 percent reduction in DSYT scores. $DSYT_F$ and PB_F scores at follow-up were controlled by their corresponding scores at baseline.

  The hypothesis was supported.

- H_{44}: There is a linear and inverse association between age and pain suffering at follow-up.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical association between age and pain suffering at baseline (Age $\rightarrow PS_F$ = -0.01, SE = 0.02, p = 0.60)

  The hypothesis was not supported.

- H_{o45}: There is no difference on follow-up pain unpleasantness ratings between males and females.

  Results from the two wave model with the digit symbol test as the dependent variable showed that there was no statistical difference in pain unpleasantness ratings between males and females at baseline (Gender $\rightarrow PU_B$ = - 0.04, SE = 0.41, p = 0.92)

  The hypothesis was supported.

- H_{o46}: There is no significant association between race and pain suffering at follow-up.

  Results from the two wave model with the DSYT as the dependent variable showed no significant difference in pain suffering ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PS_F = -0.85, SE = 0.54, p = 0.11).

  The hypothesis was supported.

- H_{o47}: There is no significant association between race and pain behavior at follow-up.

  Results from the two wave model with the DSYT as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PB_F = – 0.02, SE = 0.05, p = 0.64).

  The hypothesis was supported.

- H_{o48}: There is no significant association between age and pain behavior at follow-up.

  Results from the two-wave model with the DSYT as the dependent variable showed that there no statistical association between pain behavior and age at follow-up (Age →PB_F = 0.003, SE = 0.003, p = 0.40).

  The hypothesis was supported.

- H_{49}: There is a linear and direct association between morphine equivalent dose and pain intensity at follow-up.

  Results from the two-wave DSYT model showed that there was a statistically significant direct association between pain intensity and MED at follow-up (P MED_F → PI_F = 5.77, SE = 2.52, p = 0.02). Since a log transformation was applied to the MED_F indicator, the coefficient implies that a one percent change in MED_F is associated with a 0.057 unit change in pain intensity ratings.

  The hypothesis was supported.

- H_{50}: There is a linear and direct association between valium equivalent dose and pain suffering at follow-up.

  Results from the two-wave DSYT model showed that there was no statistical association between pain suffering and VED at baseline ($VED_F \rightarrow PS_F = 0.35$, SE = 0.21, p = 0.09). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a one percent change in VED is associated with a 0.03 unit change in PS.

- H_{51}: There is an inverse association between age and DST at follow-up.

  Results from the two-wave DSYT model showed that there was no statistically significant association between age and DSYT at follow-up (Age $\rightarrow DSYT_F = -0.003$, SE = 0.02, p = 0.15). Since a log transformation was applied to the DSYT indicator, a one year increase in age is associated with a 0.3% reduction in DSYT scores.

  The hypothesis was not supported.

4.6.5 Hypothesized Paced Auditory Serial Addition Test (PASAT) Model

The dependent variable for the PASAT model was the paced auditory serial attention test factor at baseline ($PASAT_B$) and follow-up ($PASAT_F$). The $PASAT_B$ factor was composed of two indicators, namely, lnPASAT 2.4 and lnPASAT 2.0 at baseline. The $PASAT_F$ factor was composed of two indicators, namely, lnPASAT 2.4 and lnPASAT 2.0 at follow-up. The structural component of the PASAT model can be viewed in Figure 4.11.

Structural equation modeling results (chi square = 204.20, df = 212, p = 0.65) showed that the data were an excellent fit to the model. Goodness of fit indices for the model can be viewed in Table 4.35.

Unstandardized parameter estimates of modeled associations are presented in Table 4.40

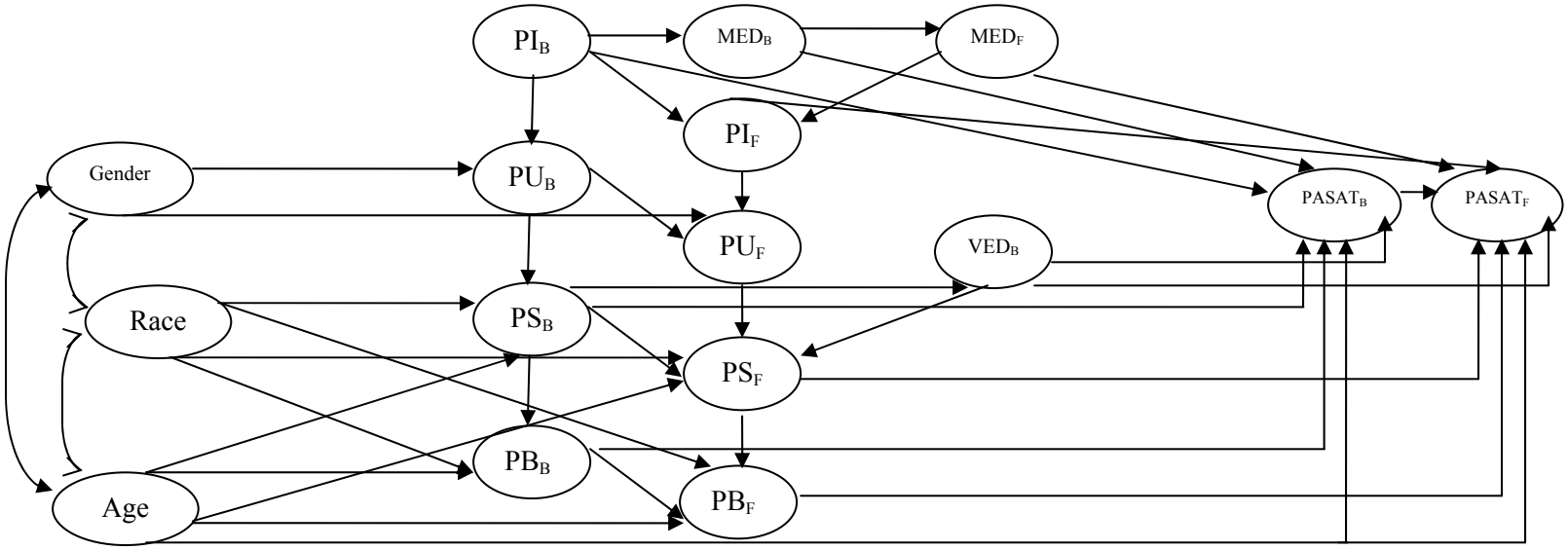
Table 4.40 Table of Unstandardized Model Equations and Squared Multiple Correlations of Paced Auditory Serial Addition Test Model

Model Equations	R^2
$PU_B = 0.30G + 1.21^{***}PI_B + 2.57^{**}D_{PUB}$	0.69
$PU_F = -0.02G + 0.95^{***}PI_F + 0.26^{*}PU_B + 1.60^{*}D_{PUF}$	0.83
$PS_B = 0.01A - 2.0^{**}E + 0.59^{***}PU_B + 10.15^{***}D_{PSB}$	0.24
$PS_F = -0.01A - 0.76E + 0.47^{***}PU_F + 0.50^{***}PS_B + 0.33VED + 4.97^{***}D_{PSF}$	0.62
$PB_B = 0.01A + 0.009E + 0.13^{***}PS_B + 0.58^{***}D_{PBB}$	0.33
$PB_F = 0.009A - 0.01E + 0.08^{***}PS_F + 0.38^{***}PB_B + 0.40^{***}D_{PBF}$	0.44
$VED = 0.05PS_B + 1.57^{***}D_{VED}$	0.02
$MED_B = 0.05PI_B + 0.26^{***}D_{MEDB}$	0.03
$MED_F = 0.64^{***}MED_B + 0.12^{***}D_{MEDF}$	0.47
$PI_F = 0.68^{***}PI_B + 3.65^{**}MED_F - 3.13^{**}MED_B + 3.00^{**}D_{PIF}$	0.53
$PASAT_B = -0.004PS_B - 0.034PB_B + 0.06MED_B - 0.064^{**}VED - 0.017PI_B + 0.05^{***}D_{PASATB}$	0.18
$PASAT_F = -0.008PS_F - 0.022PB_F - 0.033MED_F + 0.006VED - 0.005PI_F + 0.80^{***}PASAT_B + 0.01^{*}D_{PASATF}$	0.84

PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, PASAT-Paced Auditory Serial Addition Test, B-Baseline, F-Follow-up, D – Disturbance term associated with the latent variable

***p < 0.001, **p<0.01, *p<0.05

Figure 4.11 Hypothesized Two-Wave PASAT Measurement Model



PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behavior, MED-Morphine Equivalent Dose, VED-Valium Equivalent Dose, PASAT – Paced Auditory Serial Addition Test Factor, B-Baseline, F-Follow-up

4.6.5.1 Hypothesis Testing – Paced Auditory Serial Addition Test

Results from the two-wave longitudinal model with Paced Auditory Serial Addition Test (PASAT) as the dependent variable:

The proposed hypothesis and corresponding results are listed in order. All parameter estimates are expressed as unstandardized units unless specified otherwise.

A summary of the examined relationships is presented in Table 4.41:

Table 4.41 Summary of Hypothesized Relationships for the Paced Auditory Serial Addition Test Model

Model Component	Regression Weight	Significance Level	Hypothesis	Hypothesis Supported
$MED_B \rightarrow PASAT_B$	0.06	0.33	H_{o53}	Yes
$VED \rightarrow PASAT_B$	-0.06	0.008	H_{54}	Yes
$PI_B \rightarrow PASAT_B$	-0.017	0.34	H_{o55}	Yes
$PS_B \rightarrow PASAT_B$	-0.004	0.71	H_{56}	No
$PB_B \rightarrow PASAT_B$	-0.03	0.38	H_{57}	No
$A \rightarrow PS_B$	0.01	0.83	H_{58}	No
$G \rightarrow PU_B$	0.30	0.57	H_{o59}	Yes
$E \rightarrow PS_B$	-2.00	0.01	H_{o60}	No
$E \rightarrow PB_B$	0.00	0.96	H_{o61}	Yes
$A \rightarrow PB_B$	0.01	0.06	H_{o62}	Yes
$PI_B \rightarrow MED_B$	0.05	0.19	H_{63}	No
$PS_B \rightarrow VED$	0.05	0.24	H_{64}	No
$A \rightarrow PASAT_B$	-0.002	0.56	H_{65}	No
$MED_F \rightarrow PASAT_F$	-0.03	0.37	H_{o66}	Yes
$VED \rightarrow PASAT_F$	0.006	0.66	H_{67}	No
$PI_F \rightarrow PASAT_F$	-0.005	0.55	H_{o68}	Yes
$PS_F \rightarrow PASAT_F$	-0.008	0.21	H_{69}	No
$PB_F \rightarrow PASAT_F$	-0.022	0.30	H_{70}	No
$A \rightarrow PS_F$	-0.01	0.73	H_{71}	No
$G \rightarrow PU_F$	-0.02	0.94	H_{o72}	Yes
$E \rightarrow PS_F$	-0.76	0.27	H_{o73}	Yes
$E \rightarrow PB_F$	-0.01	0.95	H_{o74}	Yes
$A \rightarrow PB_F$	0.009	0.29	H_{o75}	Yes
$MED_F \rightarrow PI_F$	3.65	0.01	H_{76}	Yes
$VED \rightarrow PS_F$	0.33	0.20	H_{77}	No
$A \rightarrow PASAT_B$	-0.003 (0.002)	0.16	H_{78}	No

- Hypothesis not testable

A- Age, G – Gender, PI-Pain Intensity, PU-Pain Unpleasantness, PS-Pain Suffering, PB-Pain Behaviors, MED, Morphine Equivalent Dose, VED-Valium Equivalent Dose, PASAT-Paced Auditory Serial Addition Test, B-Baseline, F-Follow-up

- H_{o53}: There is no association between morphine equivalent dose (MED) of short-acting narcotic analgesic agents and PASAT scores at baseline.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there is no significant association between MED and PASAT scores at baseline ($MED_B \rightarrow PASAT_B$ = 0.06, SE = 0.06, p = 0.33). Since a log transformation was applied to indicators of both PASAT and MED at baseline, the coefficient implies that a one percent change in MED_B is associated with a 0.06 percent change in PASAT scores.

  The hypothesis was supported.

- H_{54}: There is a linear and inverse relationship between benzodiazepine dose and PASAT scores at baseline.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there is a significant inverse association between VED and PASAT scores at baseline ($VED \rightarrow PASAT_B$ = -0.06, SE = 0.02, p = 0.008). Since a log transformation was applied to indicators of both PASAT and VED at baseline, the coefficient implies that a one percent change in VED is associated with a 0.06 percent reduction in PASAT scores.

  The hypothesis was supported.

- H_{o55}: There is no direct association between pain intensity and PASAT scores at baseline.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there was no significant association between pain intensity ratings and PASAT scores at baseline ($PI_B \rightarrow PASAT_B$ = -0.017, SE = 0.018, p = 0.34). Since indicators for the PASAT factor were transformed utilizing a natural log transformation, the regression coefficient implies that a unit change in PI scores corresponds with a 1.8 percent reduction in PASAT scores.

The hypothesis was supported.

- H_{56}: There is a linear and inverse association between pain suffering and PASAT scores at baseline.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there is a non-significant association between pain suffering ratings and PASAT scores at baseline ($PS_B \rightarrow PASAT_B$ = -0.004, SE = 0.01, p = 0.71). Since indicators for the PASAT factor were transformed utilizing a natural log transformation, the regression coefficient implies that a unit change in PS scores corresponds with a 0.4 percent reduction in PASAT scores.

  The hypothesis was not supported.

- H_{57}: There is a linear and inverse association between frequency of pain behaviors and PASAT scores at baseline.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there is a inverse but non significant association between frequency of pain behaviors and PASAT scores at baseline ($PB_B \rightarrow PASAT_B$ = -0.03, SE = 0.03, p = 0.38). Since indicators for the PASAT factor were transformed utilizing a natural log transformation, the regression coefficient implies that a unit change in PB scores corresponds with a three percent reduction in PASAT scores.

  The hypothesis was not supported.

- H_{58}: There is a linear and inverse association between age and pain suffering scores at baseline.

  Results from the two wave model with the PASAT as the dependent variable showed that there was no statistical association between age and pain suffering at baseline (Age $\rightarrow PS_B$ = 0.01, SE = 0.04, p = 0.83)

  The hypothesis was not supported.

- H_{o59}: There is no difference in baseline pain unpleasantness ratings between males and females at baseline.

Results from the two wave model with the PASAT as the dependent variable showed no difference in pain unpleasantness ratings between males and females (Gender → $PU_B = 0.30$, SE = 0.54, p = 0.57)

The hypothesis was supported.

- H_{o60}: There is no association between ethnicity and pain suffering at baseline.

  Results from the two-wave model with the PASAT as the dependent variable showed that Caucasians provided significantly lower pain suffering ratings than patients belonging to other ethnic groups at baseline. (Ethnicity → $PS_B = -2.0$, SE = 0.54, p = 0.01).

  The hypothesis was not supported.

- H_{o61}: There is no association between ethnicity and pain behavior at baseline.

  Results from the two wave model with the PASAT as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at baseline. (Ethnicity → $PB_B = 0.009$, SE = 0.19, $p < 0.96$).

  The hypothesis was supported.

- H_{o62}: There is no significant association between age and pain behavior at baseline.

  Results from the two-wave model with the PASAT as the dependent variable showed that there no statistical association between pain behavior and age at baseline (Age →$PB_B = 0.01$, SE = 0.01, p = 0.06).

  The hypothesis was supported.

- H_{63}: There is linear and direct association between pain intensity and morphine equivalent dose at baseline.

  Results from the two-wave PASAT model showed that there was no statistical association between pain intensity and MED at baseline (PI_B→ $MED_B = 0.05$, SE = 0.03, p = 0.19). Since a natural log transformation was applied to the MED indicator, the regression

coefficient implies that a unit change in PI is associated with a five percent change in MED.

The hypothesis was not supported.

- H_{64}: There is linear and direct association between pain suffering and valium equivalent dose at baseline.

  Results from the two-wave PASAT model showed that there was no statistical association between pain suffering and VED at baseline ($PS_B \rightarrow VED_B = 0.05$, SE = 0.04, p = 0.24).). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a unit change in PS is associated with a five percent change in VED.

  The hypothesis was not supported

- H_{65}: There is an inverse association between age and PASAT at baseline.

  Results from the two-wave PASAT model showed that there was no statistically significant association between age and PASAT at baseline (Age $\rightarrow PASAT_B = -0.002$, SE = 0.003, p = 0.57). Since a log transformation was applied to the PASAT indicator, the regression coefficient implies that a one year increase in age is associated with a 0.2 percent reduction in DSYT.

  The hypothesis was not supported.

- H_{o66}: There is no association between morphine equivalent dose (MED) of Avinza® plus breakthrough medication dose and PASAT scores at follow-up.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there is a negative but non significant association between MED and PASAT scores at follow-up ($MED_F \rightarrow PASAT_F = - 0.03$, SE = 0.03, p = 0.37). Since a log transformation was applied to indicators of both PASAT and MED at baseline, the coefficient implies that a one percent change in MED_F is associated

with a 0.03 percent reduction in PASAT scores. MED_F and $PASAT_F$ scores were controlled by their corresponding scores at baseline.

The hypothesis was supported.

- H_{67}: There is a linear and inverse relationship between benzodiazepine dose and PASAT scores at follow-up.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there was no statisitical association between VED and PASAT scores at follow-up. (VED → $PASAT_{FU}$ = 0.006, SE = 0.01, p = 0.66). Since a log transformation was applied to indicators of both PASAT and VED at baseline, the coefficient implies that a one percent change in VED is associated with a 0.6 percent increase in PASAT scores. $PASAT_F$ score was controlled by its corresponding score at baseline.

  The hypothesis was not supported.

- H_{o68}: There is no direct association between pain intensity and PASAT scores at follow-up.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there was a non-significant association between PASAT scores and pain intensity ratings at follow-up. (PI_{FU} → $PASAT_{FU}$ = - 0.005, SE = 0.008, p = 0.55). Since a log transformation was applied to PASAT indicators, the coefficient implies that a one percent change in PI at follow-up is associated with a 0.5 percent reduction in PASAT scores. PASAT and PI scores at follow-up were controlled by their corresponding score at baseline.

  The hypothesis was not supported.

- H_{69}: There is a linear and inverse association between pain suffering and PASAT scores at follow-up.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there was a non-significant association

between pain suffering ratings and PASAT scores at follow-up. (PS_{FU} → $PASAT_{FU}$ = - 0.008, SE = 0.007, p = 0.21). Since a log transformation was applied to PASAT indicators, the coefficient implies that a one percent change in PS at follow-up is associated with a 0.7 percent reduction in PASAT scores. PASAT and PS scores at follow-up were controlled by their corresponding score at baseline.

The hypothesis was not supported

- H_{70}: There is a linear and inverse association between frequency of pain behaviors and PASAT scores at follow-up.

  Results from the two-wave model with PASAT scores modeled as the dependent variable showed that there was a non-significant inverse association between frequency of pain behavior ratings and PASAT scores at follow-up. (PB_{FU} → $PASAT_{FU}$ = -0.022, SE = 0.02, p = 0.30). Since a log transformation was applied to PASAT indicators, the coefficient implies that a one percent change in PB at follow-up is associated with a 2.8 percent reduction in PASAT scores. PASAT and PB scores at follow-up were controlled by their corresponding score at baseline.

  The hypothesis was supported.

- H_{71}: There is a linear and inverse association between age and pain suffering at follow-up.

  Results from the two wave model with the PASAT as the dependent variable showed that there was no statistical association between age and pain suffering atfollow-up (Age → PS_F = -0.01, SE = 0.03, p = 0.73)

  The hypothesis was not supported.

- H_{o72}: There is no difference in follow-up pain unpleasantness ratings between males and females.

Results from the two wave model with the PASAT as the dependent variable showed no difference in pain unpleasantness ratings between males and females (Gender → PU_F = - 0.02, SE = 0.42, p = 0.94)

The hypothesis was supported.

- H_{o73}: There is no association between ethnicity and pain suffering at follow-up.

  Results from the two wave model with the PASAT as the dependent variable showed no significant difference in pain suffering ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PS_F = -0.76, SE = 0.69, p = 0.27).

  The hypothesis was supported.

- H_{o74}: There is no association between ethnicity and pain behavior at baseline.

  Results from the two wave model with the PASAT as the dependent variable showed no significant difference in pain behavior ratings between those provided by Caucasians and other ethnic groups at follow-up. (Ethnicity → PB_F = -0.01, SE = 0.16, p= 0.95).

  The hypothesis was supported.

- H_{o75}: There is no significant association between age and pain behavior at follow-up.

  Results from the two-wave model with the PASAT as the dependent variable showed that there no statistical association between pain behavior and age at follow-up (Age →PB_F = 0.009, SE = 0.009, p = 0.29).

  The hypothesis was supported.

- H_{24}: There is a linear and direct association between morphine equivalent dose and pain intensity at follow-up.

  Results from the two-wave PASAT model showed that there was no statistical association between pain intensity and MED at follow-up (MED_F → PI_F = 3.65, SE = 1.12, p < 0.01). Since a log

transformation was applied to the MED_F indicator, the coefficient implies that a one percent change in MED_F is associated with a 0.036 unit change in pain intensity ratings.

The hypothesis was supported

- H_{25}: There is a linear and direct association between valium equivalent dose and pain suffering at follow-up.

  Results from the two-wave PASAT model showed that there was no statistical association between pain suffering and VED at baseline ($VED_F \rightarrow PS_F = 0.33$, SE = 0.26, p = 0.20). Since a natural log transformation was applied to the VED indicator, the regression coefficient implies that a one percent change in VED is associated with a 0.03 unit change in PS.

  The hypothesis was not supported.

- H_{76}: There is an inverse association between age and PASAT at follow-up.

  Results from the two-wave PASAT model showed that there was no statistically significant association between age and PASAT at follow-up (Age $\rightarrow PASAT_F = -0.003$, SE = 0.02, p = 0.16). Since a log transformation was applied to the PASAT indicator,

  The hypothesis was not supported.

Chapter 5: Discussion and Conclusion

The purpose of this section is to interpret the results from the previous section. The findings from the current study will be compared and contrasted with contemporary research in the field. The relevance of the findings will be discussed in reference to chronic pain patients and the pain management community at large. The chapter is composed of a discussion of all the modeled variables. This discussion is followed by a contrast of the stages of pain model confirmed by the current data with Wade's previously published model. Subsequently, the associations between the dependent variables for each model, i.e., DST, DSYT, and PASAT models and their predictors are examined. Finally, limitations of the study are addressed, and conclusions drawn from the aforementioned discussion.

5.1 Study Withdrawals

The proportion of patients who withdrew from this study (21.7%, n = 28) due to an adverse event (excluding inadequate pain control) was similar to a double-blind, placebo controlled study which assessed the safety and efficacy of Avinza®. The proportion of patients who withdrew due to an adverse event (excluding "lack of efficacy") from the latter study was 23.9 percent.[317]

Common adverse events that contributed to withdrawals from the study were drowsiness (n = 14), fatigue (n= 8), and nausea (n = 5). The frequent incidence of an allergic type reaction [allergies to morphine (n = 6), itching (n = 6), shortness of breath (n = 2), and rashes (n = 2)) suggested that pain patients should be screened for morphine sensitivity prior to treatment with Avinza® or other morphine agents.

Except for gender, evaluable and non-evaluable patients were comparable on demographic characteristics such as age, ethnicity, and education. Non-evaluable

[317] Caldwell JR, Rapoport RJ, Davis JC et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. Journal of Pain and Symptom Management. 2002;23:278-291.

patients used significantly higher doses of short-acting narcotics at baseline than evaluable patients. Patients who withdrew from the study reported significantly higher ratings on items assessing negative emotions than patients who completed the study. These patients reported a significantly greater reduction in home- and family-related responsibilities. Non-evaluable patients tended to score lower on the administered tests of attention; a significant difference was observed between evaluable and non-evaluable patients on the PASAT 2.0.

These differences do not suggest systematic differences between evaluable and non-evaluable patients. It can be speculated that the lack of a significant statistical association between pain suffering and tests of cognitive function may be attributable to patients who were lost to follow-up.

5.2 Key model Variables

5.2.1 Morphine Equivalent Dose (MED)

All patients enrolled in the study were utilizing a short-acting narcotic dose at the time of enrollment. The average short-acting narcotic analgesic morphine equivalent dose (MED) utilized by evaluable patients at baseline was 52.39 mg. The average narcotic dose from baseline to follow-up increased by 58.0 percent. At the end of one-month follow-up, patients had been stabilized on an average Avinza® dose of 59.11mg. Average breakthrough pain medication MED at follow-up was 23.68mg.

5.2.2 Valium Equivalent Dose (VED)

Benzodiazepines are frequently prescribed in the treatment of chronic non-malignant pain. Greater than a third of evaluable patients (34.7%) were prescribed benzodiazepines. The average daily Valium equivalent dose (VED) utilized by evaluable patients at baseline and follow-up was 16.81 mg. A negative dose-response association between benzodiazepine use and performance on tests of cognitive function has been

established.[318,319] Previous studies that examined the association between narcotic use and cognitive function failed to control for the confounding effects of benzodiazepines.[320,321] Inclusion of this confounder in the present analysis enabled the delineation of associations between narcotics and cognitive function while controlling for the effects of benzodiazepine dose.

Results from this study indicated a negative association between benzodiazepine dose and tests of cognitive function (digit symbol and paced auditory serial addition test). These associations are addressed later in the chapter.

5.2.3 Pain Intensity

Baseline and follow-up assessments of patient-reported pain intensity at the highest, lowest, and usual levels in the previous week were made. Following a four-week trial with Avinza, evaluable patients reported an average reduction of 14.2 percent, 32.2 percent, and 23.7 percent in pain at the highest, lowest, and usual pain intensity levels, respectively. The average pain intensity levels reported at follow-up were significantly lower ($p < 0.05$) than those reported at baseline.

The results were comparable with an efficacy study, which showed an average reduction of 26.7 percent (qAM dosing) and 22.8 percent (qPM dosing) after a four-week trial with Avinza.[322] All patients in the current study were recommended to follow an "AM" dosing schedule.

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[318] Scheman J, Aker R, Covington E. Cognitive effects of opioid and benzodiazepine weaning. Abstract. *American Pain Society*. 2003;Poster# 859. http://www.ampainsoc.org/abstract/2003/data/859/index.html. Accessed:Jun 11, 2003.

[319] Curran KC, Marks HN, Basoglu M. Long-term effects of alprazolam on memory: a 3.5 year follow-up of agrophobia/panic patients. *Psychological Medicine*. 1999;29:225-231.

[320] Haythornthwaite JA, Lynette MA, Quatrano-Piacentini Al, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *Journal of Pain and Symptom Management*. 1998;15:185-194.

[321] Francis SE. The effects of long term opioid therapy on neuropsychological functioning in chronic pain patients. California Institue of Integral Studies. Dissertation. June 1999; 130p

[322] Caldwell JR, Rapoport RJ, Davis JC et al. Efficacy and safety of a once-daily morphine formulation in chronic, moderate-to-severe osteoarthritis pain: results from a randomized, placebo-controlled, double-blind trial and an open-label extension trial. Journal of Pain and Symptom Management. 2002;23:278-291.

5.2.4 Pain Unpleasantness

Baseline and follow-up assessments of patient-reported pain unpleasantness at the highest, lowest, and usual pain intensity levels in the previous week were made. Following a four-week trial with Avinza, evaluable patients reported an average reduction of 13.6 percent, 37.6 percent, and 24.7 percent in pain unpleasantness at the highest, lowest and usual pain intensity levels, respectively. The average pain unpleasantness levels reported at follow-up were significantly lower ($p < 0.05$) than those reported at baseline.

5.2.5 Pain Suffering

The original pain suffering construct was composed of negative emotions and negative beliefs.

5.2.5.1 Negative Emotions

Negative emotions were assessed by asking patients to rate the intensity of each emotion, i.e., depression, anxiety, frustration, anger, and fear in the context of their pain. A significant reduction ($p < 0.05$) in the average rating for each emotion was observed at follow-up. Following a four-week trial with Avinza, evaluable patients reported an average reduction of 15.1 percent in depression, 20.5 percent in anxiety, 19.0 percent in frustration, 29.6 percent in anger, and 15.7 percent in fear.

5.2.5.2 Negative Beliefs

On average, the levels of negative beliefs at follow-up were lower than those reported at baseline. Evaluable patients believed that, on average, interference due to pain reduced by 22.2 percent and difficulty to endure pain reduced by 20.2 percent. Treatment with Avinza, a long-acting morphine agent, enhanced patients' belief in their

ability to control pain. Patients reported that their ability to control pain following a four-week trial with Avinza increased by 28.0 percent.

5.2.6 Pain Behaviors

Pain Behaviors were assessed through five items on the psychological pain inventory (PPI). Of these five items, a significant ($p < 0.05$) reduction from baseline to follow-up was seen for frequency of pain behaviors at home (mean reduction = 0.36) and observed pain behaviors (mean reduction = 0.48). The average reduction/improvement in pain behaviors observed for the other indicators was small and not significant. The average reduction in mean scores for social reinforcement of pain behaviors, home or family related responsibilities, and pain contingent down time was 0.08, 0.07, and 0.15, respectively.

As described in the results section, raw scores for each pain behavior indicator were collapsed to form categories that ranged from zero to three. Often, meaningful information may not be discernable when continuous data is collapsed to form categories. A comparison between baseline and follow-up raw scores before data were collapsed into categories showed meaningful differences for the two other indicators used to form the pain behaviors construct. A paired-samples t-test ($t = 3.55$, $df = 83$, $p < 0.001$) showed that patient mean scores on the pain or family related responsibilities scale were significantly lower at follow-up (mean = 7.45, sd = 4.5) compared to baseline (mean = 8.30, sd = 5.1). Similarly, a paired sample t-test showed that there was a significant decrease ($t = 4.02$, $df = 83$, $p < 0.01$) in average scores on the item which assessed pain contingent down time. The mean pain contingent downtime decreased from baseline (mean = 3.71 hours) to follow-up (mean = 2.55 hours).

5.2.7 Digit Span Test (DST)

The digit symbol test (DST) is composed of the digits forward and backward tests. Scores for each test are calculated as the total number of series recalled correctly

before an individual fails to recall two consecutive series of numbers with the same length. A total score for the test is calculated by summing the scores of the two individual tests.

A significant ($t = 5.17$, $df = 83$, $p < 0.01$) improvement in total span was observed from baseline to follow-up. Average total span on the test increased from 16.14 at baseline to 17.60 at follow-up for evaluable patients.

Since this study did not employ a control group, the improvement in scores from baseline to follow-up may be an artifact due to the effect of regression to the mean. In order to test for this effect, baseline and follow-up scores on the digits forward and backward tests were compared for participants who scored one standard deviation above and below the mean score for each test at baseline. This strategy was undertaken since post-test scores have a tendency to regress to the mean, i.e., cases with below average pre-intervention test scores tend to have higher post-intervention test scores and cases with above average pre-intervention test scores tend to the mean on the posttest.

Data in Table 5.1 suggests that a small regression to the mean effect may be operating. Regression to the mean is a function of the initial score (deviation from mean) and the test retest reliability or lack thereof. An estimate of the retest score can be calculated using the formula[323]:

$$\text{Estimated } S_F = CM + R\,(\text{Score}_F - \text{Score}_B) \quad \ldots\ldots\ldots\ldots \text{Eqn 5.1}$$

CM or common mean is the average of mean scores at baseline and follow-up. R is a measure of test-retest reliability obtained from the literature. S_F represents the estimated score at follow-up or retest score. The subscripts F and B denote follow-up and baseline scores. The common mean for the digits forward and backward tests were 9.81 and 7.06, respectively. The test-retest reliability for the tests reported in the literature range from 0.66 to 0.89 (Table 1.2).

An estimated retest score was calculated for each individual with a baseline mean score that was ≥ one standard deviation above the baseline mean score for both tests. The mean estimated retest score for this group of individuals on the digits forward test ranged

[323] Streiner DL. Regression toward the mean: its etiology, diagnosis, and treatment. *Canadian Journal of Psychiatry*. 2001;46:72-77.

from 11.86 to 12.53 using 0.66 and 0.89 as reliability estimates, respectively. The average estimated retest score for patients with mean baseline digits backward test scores that were ≥ one standard deviation above the mean ranged from 9.0 to 9.67. In the case of both tests, the observed means (Table 5.1) were slightly greater than the upper limit of the estimated retest scores. Since the observed retest score was greater than the upper limit of the predicted score, it may be concluded that effects of regression to the mean in this sample for digit span test scores are limited.

Table 5.1 Mean Baseline and Follow-up Scores of Evaluable Patients with Scores that were One Standard Deviation Above and below (1SD ≥ Mean ≤ 1SD) the Mean Sample Baseline Digits Span Forwards and Backwards Test Scores

	Patients who Scored 1 SD Above Sample Mean		Patients who Scored 1 SD Below Sample Mean	
	$Mean_B$	$Mean_F$	$Mean_B$	$Mean_F$
DST - Forward	12.92	12.64	6.43	7.93
DST - Backward	10.0	9.69	3.87	5.0

SD – standard deviation
B – Baseline
F- Follow-up
DST – Digit Span Test

5.2.8 Digit Symbol Test (DSYT)

The digit symbol test (DSYT), like the DST, is a subtest of the Wechsler Adult Intelligence Scale – Third Edition (WAIS – III). The average score on the DSYT increased by 5.4 percent, which was statistically significant ($p < 0.01$). Baseline and follow-up scores on the digit symbol test were compared for participants who scored one standard deviation above and below the mean digit symbol test score for all participants at baseline. Again, data presented in Table 5.2 suggest that a regression to the mean effect may be operating here.

Thus, an estimated retest score was calculated for patients with mean baseline scores that were greater than or equal to one standard deviation above the mean baseline

DSYT score. The common mean for the baseline and follow-up tests was 63.8 and test-retest reliability estimates ranged from 0.82 to 0.89.

Using equation 5.1, estimates of the average retest scores ranged from 82.99 to 84.63 with reliability estimates ranging from 0.82 and 0.89, respectively. Since the observed retest score (table 5.2) was greater than the upper limit of the predicted score, the possibility of a regression to the mean effect was questionable.

Table 5.2 Mean Baseline and Follow-up Scores of Evaluable Patients with Scores that were One Standard Deviation Above and below (1SD ≥ Mean ≤ 1SD) the Mean Sample Baseline Digits Symbol Test Scores

	Patients who Scored ≥ 1 SD over Sample Mean		Patients who Scored ≤ 1 SD Below Sample Mean	
	$Mean_B$	$Mean_F$	$Mean_B$	$Mean_F$
DSYT	87.21	85.36	38.0	42.08

SD – standard deviation
B – Baseline
F- Follow-up
DSYT – Digit Symbol Test

5.2.9 Paced Auditory Serial Addition Test (PASAT)

The PASAT tests were assessed at two presentation rates, i.e., 2.4 and 2.0 second presentation rates. The number of correct responses at baseline and follow-up were calculated for each presentation rate. The score on the PASAT 2.4 improved significantly from baseline to follow-up (mean difference = 4.69, $t = 7.15$, $df = 81$, $p < 0.01$). Similarly, the score on the PASAT 2.0 improved significantly from baseline to follow-up (mean difference = 3.89, $t = 5.6$, $df = 81$, $p < 0.01$).

Baseline and follow-up scores on the PASAT 2.4 and 2.0 were compared for participants who scored one standard deviation above and below the mean PASAT 2.4 and 2.0 scores for all participants at baseline. As shown in table 5.3, follow-up mean PASAT 2.4 scores was higher than baseline scores for both groups of individuals. Thus,

it can be concluded that the effect of regression to the mean was not operating in this instance.

In the case of the PASAT 2.0, there was a very small decline (-0.13) in mean follow-up scores of individuals with baseline mean scores that were greater than one standard deviation above the mean baseline score of all participants. This result suggested that the effect of regression to the mean was not operating.

Table 5.3 Mean Baseline and Follow-up Scores of Evaluable Patients with Scores that were One Standard Deviation Above and below (1SD ≥ Mean ≤ 1SD) the Mean Sample Baseline PASAT 2.4 and 2.0 Scores

	Patients who Scored 1 SD Above Sample Mean		Patients who Scored 1 SD Below Sample Mean	
	$Mean_B$	$Mean_F$	$Mean_B$	$Mean_F$
PASAT 2.4	45.94	47.22	21.50	28.22
PASAT 2.0	45.69	45.56	19.5	26.29

SD – standard deviation
B – Baseline
F- Follow-up

In summary, follow-up measures of pain intensity, pain unpleasantness, pain suffering and pain behaviors were lower than those reported at baseline. Average daily narcotic dose increased from baseline to follow-up. There was an improvement in performance on tests assessing cognitive function. The improvement in test scores from baseline to follow-up was not entirely independent of the effects of regression to the mean.

5.3 Stages of Pain Model

This section is confined to the discussion of results from the confirmatory factor analysis procedure of the stages of pain model. Results from the current data supported a four factor structure for the stages of pain model. The four factors that represent different stages of the model are: pain intensity (stage I), pain unpleasantness (stage II), pain suffering (stage III) and pain behaviors (stage IV). However, the measurement components of the model varied from previously published measurement models of the stages of pain model.

Wade and colleagues confirmed a four factor solution for the stages of pain model.[324] The pain intensity and pain unpleasantness factors were composed of average pain intensity and average pain unpleasantness in the previous week, respectively. The pain suffering factor was composed of five indicators, namely, depression, frustration, anxiety, anger and fear. Pain behavior in the home, social reinforcement of pain behavior, home or family related responsibilities and observed pain behaviors represented the pain behavior factor.

In a subsequent study, Riley, Wade and colleagues examined the association between race/ethnic background and stages of pain model variables.[325] The composition of the pain behavior factor in this study varied slightly from the previously confirmed model. The 'observed pain behaviors' indicator was replaced by the indicator which assessed 'pain contingent down time.'

The results from this study found support for a re-specification of the stages of pain models described above. The stages of pain model – modification 2 with baseline data was similar to the above models, except for the indicators used to form the pain behavior factor. The pain behavior factor for this model (modification 2) included three

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[324] Wade JB, Dougherty LM, Archer CR, Price DD. Assessing the stages of pain processing: a multivariate analytical approach. *Pain*. 1996;68:157-167.

[325] Riley JL, Wade JB, Myers CD et al. Racial/ethnic differences in the experience of chronic pain. Pain. 2002;100:291-298**.**

indicators: pain behaviors at home, home or family related responsibilities, and pain contingent down time.

The stages of pain model – modification 2 did not fit the data at follow-up. At follow-up, residual variances for three indicators of the pain suffering construct were negative (frustration, anger, fear). The negative variances were contributing to model misspecification. The final model specified without these indicators was found to fit the data well.

Thus, the final stages of pain model determined from the data in this study differed from previously confirmed models with respect to the pain suffering and pain behavior constructs. The pain suffering factor predicted two indicators: depression and anxiety. The pain behaviors factor predicted three indicators: pain behaviors at home, home or family related responsibilities, and pain contingent down time. It is likely that a larger sample ($n > 300$) may have resulted in the confirmation of previously published models.

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5.3.1 Pain Intensity and Pain Unpleasantness

Pain intensity (stage I) is composed of the sensory-discriminative aspect of pain. Pain unpleasantness (stage II) is composed of the immediate concern regarding the pain on an individual's mental state. These two factors comprise the sensory-affective dimension of pain. A significant direct association between pain intensity and pain unpleasantness was found at baseline ($\beta = 1.11$, $p < 0.01$) and follow-up ($\beta = 1.08$, $p < 0.01$).

5.3.2 Pain Suffering

Pain suffering (stage III) is a cognitive process reflective of the emotional disruption due to chronic pain. The results showed that this stage is distinctly different from the immediate negative affect described above. A strong association was found

between pain affect/unpleasantness and pain suffering at baseline ($\beta = 0.69$, $p < 0.01$) and follow-up ($\beta = 0.65$, $p < 0.01$).

It was postulated that negative emotions arising due to chronic pain are accompanied by an individual's belief about the impact of pain in their life. This hypothesis was not supported by the current model.

This does not imply that the relationship between pain suffering and pain beliefs does not exist. Numerous studies have shown the association between these two constructs.[326,327,328] Low reliability (cronbach's $\alpha = 0.36$) for items used to measure the pain beliefs construct at baseline highlights the deficiency of the pain beliefs scale used in this study.

The stages of pain model could improve significantly by utilizing a reliable and valid measure of pain beliefs such as the pain beliefs and perceptions inventory (PBPI). The PBPI was correlated with pain related anxiety, depressive symptoms, and subjective reports of pain.[329]

The causal direction of the relationship between pain suffering and pain beliefs is not apparent. Most often, pain beliefs are conceptualized as influencing psychological symptoms. Negative beliefs and emotions may arise together influencing each other simultaneously. Thus, future studies utilizing the stages of pain model should attempt to elucidate the association between pain beliefs and pain suffering in larger samples.

5.3.3 Pain Behaviors

To a large extent, pain behaviors are the only observable components of the pain process. Functional impairment, disability, and withdrawal from usual responsibilities may be used to operationalize the concept of pain behaviors. There was a weak

[326] Williams DA, Robinson ME, Geisser ME. Pain beliefs: assessment and utility. *Pain.* 1994;59:71-78.
[327] Gibson JS, Helme RD. Cognitive factors and the experience of pain and suffering in older persons. *Pain.* 2000;85:375-383.
[328] Ashgari A, Nicholas MK. Pain self-efficacy beliefs and pain behaviors. A prospective study. *Pain.* 2001;94:85-100.
[329] Williams DA, Robinson ME, Geisser ME. Pain beliefs: assessment and utility. *Pain.* 1994;59:71-78.

relationship between pain suffering and pain behaviors at baseline (0.13) and follow-up; however, the associations at both points in time were significant ($p < 0.01$).

In order to visualize the association between pain behaviors and the indicators of the pain suffering construct, a composite pain behavior variable at baseline was created using the three indicators used to form the pain behavior construct. The composite was created by summing scores of individuals for frequency of pain behaviors at home, home- or family-related responsibilities, and pain continent down time. The sum of scores was divided by three. Greater frequency of pain behaviors (higher scores on the composite) was associated with higher levels of depression and anxiety. This trend was observed across all levels of pain behavior except for the groups of patients with a pain behavior composite score that equaled one (Figure 5.1). This groups consisted of only two patients, and corresponding data were skewed since one patient provided maximum ratings on both the depression and anxiety scales.

Figure 5.1 Plot of Depression and Anxiety by Pain Behavior Composite at Baseline

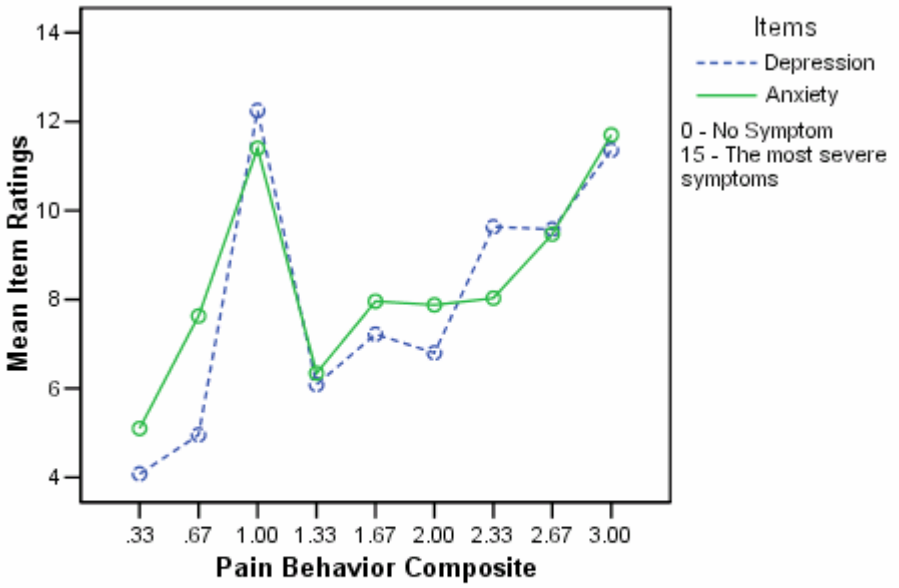
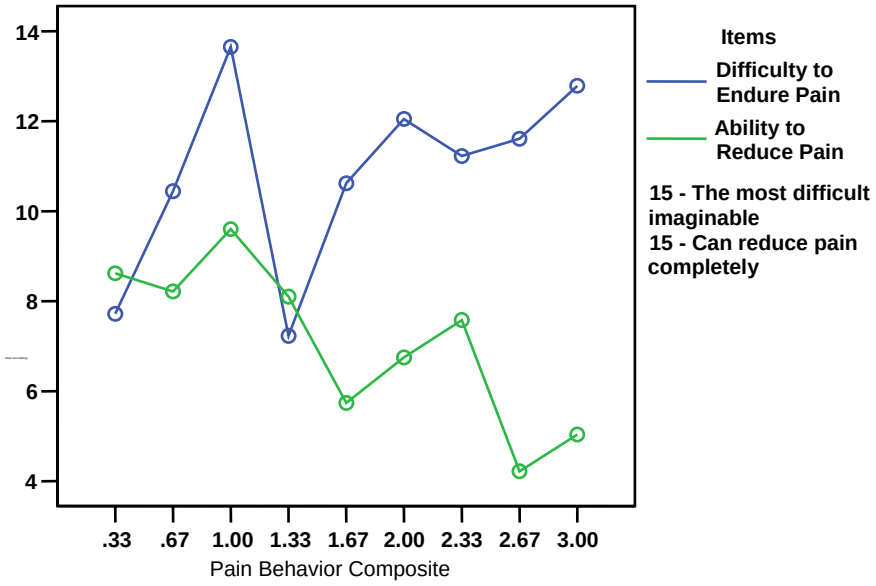


Figure 5.1 Plot of Depression and Anxiety by Pain Behavior Composite at Baseline

Prior research has also demonstrated that patients with positive perceptions about pain or patients demonstrating higher levels of self efficacy were less likely to engage in pain behaviors.[330,331] The results from this study echoed the findings from the literature.

This statement can be verified graphically from the plot of the pain behavior composite by pain belief indicators (Figure 5.2). The pain belief indicators depicted here are difficulty in enduring pain and ability to control pain. The plot clearly shows that patients with a higher frequency of pain behaviors believe that it is more difficult to endure pain and also believe that they lack the ability to endure pain. Again, an anomaly in the trend was observed for the group with a pain behavior composite score that equaled one due to extreme scores provided by one out of two patients in the group.

Figure 5.2 Plot of Ability to Endure Pain and Reduce Pain by Pain Behavior Composite at Baseline



[330] Denison E, Asenlof P, Lindberg P. Self-efficacy, fear avoidance, and pain intensity as predictors of disability in subacute and chronic musculoskeletal pain patients in primary health care. *Pain.* 2004;111:245-252.

[331] Arnstein P, Caudill M, Mandle CL, et al. Self efficacy as a mediator of the relationship between pain intensity, disability, and depression in chronic pain patients. *Pain.* 1999;80:482-491.

Thus, Figures 5.1 and 5.2 clearly show the associations between pain suffering, pain beliefs, and pain behaviors. In addition to experiencing immediate negative affect, disability due to pain occurs almost immediately. A plausible alternate hypothesis is that pain behaviors and pain beliefs arise simultaneously. Thus, an alternative progression of these relationships may exist in the context of chronic pain.

Patients with high self-efficacy levels and positive beliefs obtain control over their environment through behavioral and cognitive means.[332] The perceived control enables these patients to minimize stress and the level of threat associated with stressful events. Consequently, self-efficacious pain patients can motivate themselves to minimize the impact of pain on their behaviors and thereby limit functional impairment. Conversely, pain patients with low self-efficacy levels experience constant pain and lack an ability to control the pain. As a result, inefficacious patients are overwhelmed by stress and the associated threat, which leads to pain behaviors and functional impairment. Threat has also been shown to capture attention, thereby diverting cognitive resources.[333] The constant stress over time, lack of control, and functional impairments contribute to distress and pain suffering. This reasoning suggests that the stages of pain model in its current form may not be a reasonable explanation for "real-world" phenomena.

An alternative specification would be to model pain behaviors as a predictor of suffering. It could be hypothesized that disability due to pain may have a significant impact on an individual's psychological well-being. Empirical tests of these cause-effect relationships would enable practitioners to root cause problems and manage patients effectively by targeting the source of the problem. Secondly, inclusion of measures of pain beliefs or self-efficacy in such a model is critical, since self efficacy mediates the association between pain, functional impairment or disability, and psychological functioning in pain patients.

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[332] Bandura A, Cioffi D, Barr T, Brouillard ME. Perceived self-efficacy in coping with cognitive stressors and opioid activation. *Journal of Personality and Social Psychology*. 1988;55:479-488.
[333] Kostner EHW, Crombez G, Van Damme S, et al. Does imminent threat capture and hold attention. *Emotion*. 2004;4:312-317.

5.4 Hypothesized Models

This section examines the associations between the dependent variables in the study, i.e., tests of cognitive function and their predictors. Thus, for each of the three hypothesized models (DST, DSYT, and PASAT), associations between each predictor variable (MED, VED, pain intensity, pain suffering, and pain behaviors) and the dependent variable is examined. The association between age and tests of cognitive function, gender and pain unpleasantness, and ethnicity and pain suffering will be delineated as well.

5.4.1 Association between Morphine Equivalent Dose and Tests of Cognitive Function (DST, DSYT, and PASAT)

The primary purpose of this study was to examine the association between Avinza and performance on tests of cognitive function.

Two-Wave Digit Span Test Model

Results from the two-wave DST model showed a positive association between short-acting narcotic dose and DST scores, which approached significance ($p = 0.06$) at baseline. A ten percent change in MED was associated with a 0.068 unit change in DST scores. A statistically insignificant ($p = 0.53$) negative association was found between follow-up narcotic dose (sum of Avinza and breakthrough pain medication morphine equivalent dose) and DST scores. A ten percent change in MED was associated with a 0.038 reduction in DST scores. The results suggest that narcotics used in this study to manage chronic pain did not impair performance on the digit span test.

Two-Wave Digit Symbol Test Model

Results from the two-wave DSYT model showed a positive non-significant ($p = 0.23$) association between short-acting narcotic dose and DSYT scores. A ten percent change in MED at baseline was associated with a 0.7 percent change in DSYT scores. The association between narcotic dose at follow-up (sum of Avinza and breakthrough pain medication morphine equivalent dose) and DSYT scores was negative, but

statistically insignificant (p = 0.85). A ten percent increase in MED at follow-up was associated with a 0.08 percent reduction in DSYT scores. The results suggested that narcotics used in this study to manage chronic pain did not impair performance on the digit symbol test.

Two-Wave Paced Auditory Serial Addition Test Model

Results from the two-wave PASAT model showed a positive and non-significant association between short-acting narcotic dose and PASAT scores (p = 0.33) at baseline. A ten percent change in MED scores at baseline was associated with a 0.6 percent change in PASAT scores. The association between narcotic dose at follow-up (sum of Avinza and breakthrough pain medication morphine equivalent dose) and PASAT scores was negative, but statistically insignificant (p = 0.37). A ten percent change in MED at follow-up was associated with a 0.3 percent reduction in PASAT scored. The results suggest that narcotics used in this study to manage chronic pain did not impair performance on the paced auditory serial addition test.

There was no significant direct association between morphine equivalent dose (MED) of either short-acting or long-acting narcotics and measures of attention (DST, DSYT, and PASAT) while controlling for pain intensity, pain unpleasantness, pain suffering, pain behaviors and benzodiazepine dose. This finding was consistent with recent literature, which has demonstrated that narcotic analgesics do not impair cognitive function.[334,335,336,337] Additionally, a recent review of studies which examined the association between opioid use and cognitive function reinforced support for the finding that narcotic agents do not have detrimental effect on neuropsychological functioning.[338]

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[334] Lorenz J, Beck H, Bromm B. Cogntive performance, mood and experimental pain before and during morphine-induced analgesia in patients with chronic non-malignant pain. Pain. 1997;73:369-375.
[335] Haythornthwaite JA, Lynette MA, Quatrano-Piacentini Al, Pappagallo M. Outcome of chronic opioid therapy for non-cancer pain. *Journal of Pain and Symptom Management*. 1998;15:185-194.
[336] Rowbotham MC, Twilling L, Davies PS, et al. Oral opioid therapy for chronic peripheral and central neuropathic pain. *New England Journal of Medicine*. 2003;348:12223-1232.
[337] Raja SN, Haythornthwaite JA, Pappagallo M, et al. Opioids versus antidepressants in postherpetic neuralgia: A randomized placebo-controlled trial. *Neurology*. 2002;59:1015-1021.
[338] Ersek M, Cherrier MM, Overman SS, Irving GA. The cognitive effects of opioids. *Pain Management Nursing.* 2004;5:75-93.

5.4.2 Association between Valium Equivalent Dose, DST, DSYT, and PASAT

The second objective in this study was to examine the association between benzodiazepine use and performance on tests of cognitive function.

Two-wave Digit Span Test Model

A ten percent increase in VED was associated with a 0.001 unit reduction in DST scores. The negative association between VED and DST scores at baseline was statistically insignificant (p = 0.91). The direction and magnitude of the association did not change appreciably at follow-up. A 10 percent increase in VED was associated with a 0.005 unit reduction in DST scores. The negative association between valium equivalent dose and DST scores at follow-up was not statistically significant (p = 0.70).

Previous research has demonstrated that duration of benzodiazepine use is associated with impaired performance on neuropsychological tests.[339] In order to test these findings, a benzodiazepine use factor was created. The hypothesized DST model was modified by adding including duration of benzodiazepine use along with valium equivalent dose as two indicators, which were loaded on a factor named, "benzodiazepine use."

The model was retested with a benzodiazepine use factor that included benzodiazepine dose and duration of use as indicators. According to the exact chi-square fit test (chi-square = 231.86, p = 0.54, df = 235), model fit with the benzodiazepine use factor was adequate. The results from this model showed that a ten percent increase in this factor score was associated with a 0.003 and 0.002 reduction in DST scores at baseline and follow-up, respectively. The association between benzodiazepine use factor and DST at baseline (0.79) and follow-up (0.09) were not significant.

Thus, benzodiazepine use and benzodiazepine dose were not associated with an impaired performance on the digit span test.

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[339] Golombok S, Moodley P, Lader M. Cognitve impairment in long-term benzodiazepine users. *Psychological Medicine*. 1988;18:365-74.

Two-wave Digit Symbol Test Model

The negative association between VED and DSYT scores at baseline was statistically significant ($p = 0.03$). A ten percent increase in VED was associated with a 0.5 percent reduction in DSYT scores. The direction of the association (0.012) was positive and not significant ($p = 0.33$) at follow-up.

The model was retested with the benzodiazepine use factor that included benzodiazepine dose and duration of use as indicators. According to the exact chi-square fit test (chi-square = 232.2, $p = 0.03$, df = 194), model fit with the benzodiazepine use factor was not adequate. The negative association between the benzodiazepine use factor and DSYT scores was statistically significant ($p = 0.01$) at baseline. A ten percent increase in benzodiazepine factor scores was associated with a 0.6 percent reduction in DSYT scores. The direction of this association at follow-up was reversed (0.01) and the association was not significant ($p = 0.36$).

The proportion of variance explained for the DSYT factor at baseline in the hypothesized model and model with benzodiazepine use factor was 0.34 and 0.23, respectively. These values at follow-up were 0.88 and 0.83, respectively. Although the addition of the duration of use indicator increased the magnitude of association with DSYT scores from 0.5 to 0.6 percent, this increase was minimal. The addition of a second indicator also resulted in an ill-fitting model ($p < 0.05$) Thus, the empirical evidence suggested that the hypothesized conceptualization of the digit symbol model is appropriate. The exclusion of the duration of benzodiazepine use indicator was justified. The results indicated that increase in benzodiazepine dose was associated with an impaired performance on the digit symbol test.

Two-Wave Paced Auditory Serial Addition Test Model

The negative association between VED and PASAT scores at baseline was statistically significant ($p = 0.008$). A ten percent increase in VED was associated with a 0.6 percent reduction in DSYT scores. The direction of the association (0.006) was positive and not significant ($p = 0.66$) at follow-up.

The model was retested with the benzodiazepine use factor, which included benzodiazepine dose and duration of use as indicators. According to the exact chi-square fit test (chi-square = 249.1, p = 0.26, df = 236), model fit with the benzodiazepine use factor was adequate. The negative association between the benzodiazepine use factor and DSYT scores was statistically significant (p = 0.01) at baseline. A ten percent increase in benzodiazepine use factor scores was associated with a 0.6 percent reduction in DSYT scores. The direction of this association at follow-up was reversed (0.004) and the association was not significant (p = 0.79).

These results suggested that addition of the benzodiazepine duration of use indicator did not add any new information to the hypothesized model which included only the benzodiazepine dose indicator. Thus, use of the benzodiazepine dose factor with a single indicator, i.e., valium equivalent dose, was justifiable.

The results indicated that increase in benzodiazepine dose was associated with an impaired performance on the paced auditory serial addition test. An increase in benzodiazepine dose adversely affects the ability to maintain visual attention and motor persistence (DSYT). Additionally, an increase in benzodiazepine dose is associated with an impaired ability to adequately process information and maintain sustained and divided attention (PASAT). Benzodiazepine dose did not change from baseline to follow-up. The finding that the association between benzodiazepine dose and DST and benzodiazepine dose and PASAT scores at follow-up was positive and not significant suggests an improvement in DST and PASAT scores independent of the benzodiazepine dose. The literature review showed that studies have failed to control for the effects of benzodiazepine use in examining the association of pain on cognitive function. Recent research also fails to address this shortcoming.[340,341] A strategy of solely prescribing benzodiazepines to address pain-related anxiety is clearly not sufficient. Sources of anxiety in chronic pain and their management is an area of research in itself that must be addressed.

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[340] Apkarian AV, Sosa Y, Krauss B et al. Chronic pain patients are impaired on an emotional decision making task. *Pain*. 2004;108:129-136.

[341] Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. *Arthritis and Rheumatism.* 2002;47:639-644.

5.4.3 Association between Pain Intensity, DST, DSYT and PASAT

The third objective of this study was to determine the association between pain intensity and cognitive function test scores.

Two-wave DST Model

The association between pain intensity and DST scores was not significant. The direct (β = -0.06) and indirect (β = -0.05) association between pain intensity and DST scores at baseline were negative. A negative indirect association (β = -0.16) was found between pain intensity scores at baseline on DST scores at follow-up. The direct effect of pain intensity on DST scores at follow-up was positive (β = 0.02) and the indirect effect was zero.

Two-wave DSYT Model

The association between pain intensity and DSYT scores was not significant. A unit change in the pain intensity at baseline was associated with a 0.7 percent decline in DSYT scores at baseline. The indirect effect of pain intensity at baseline on DSYT scores at baseline was zero. A negative indirect association was found between baseline pain intensity scores and follow-up DSYT scores. A unit change in pain intensity at baseline resulted in a 0.5 percent reduction in DSYT scores at follow-up. The direct association between follow-up pain intensity ratings and DSYT scores was zero, while the indirect effect was positive. A unit change in pain intensity ratings at follow-up was associated with an indirect effect that resulted in a 0.1 percent change in DSYT scores.

Two-wave PASAT Model

The association between pain intensity and PASAT scores was not significant A unit change in pain intensity at baseline was associated with a direct effect that resulted in a 1.7 percent decline in PASAT scores at baseline. Due to an indirect effect, a unit change in pain intensity ratings at baseline resulted in a 0.6 percent decline in PASAT scores at baseline. Due to an indirect effect, a unit change in pain intensity ratings at baseline resulted in a 2.5 percent reduction in PASAT scores at follow-up. The total

effect of pain intensity ratings at follow-up on PASAT scores at follow-up was zero, since the direct effect (+ 0.5) and indirect effect (-0.5) cancelled each other out.

Similar to previous studies, no significant direct associations were found between pain intensity and cognitive test scores. The direction of the direct association between pain intensity ratings and cognitive function test scores went from being negative at baseline to positive at follow-up.

5.4.4. Association between Pain Suffering, DST, DSYT, and PASAT

The fourth objective of the study was to determine the association between pain suffering and cognitive function test.

Two-Wave Digit Span Test Model

The association between pain suffering and DST scores at baseline ($p = 0.46$) and follow-up ($p = 0.70$) was not significant. Although the association between pain suffering and digit span test scores was negative at baseline ($\beta = - 0.05$) and follow-up ($\beta = - 0.02$), the magnitude of the negative association declined from baseline to follow-up.

Two-Wave Digit Symbol Test Model

The association between pain suffering and digit symbol test scores was not significant at baseline ($p = 0.72$) and follow-up ($p = 0.90$). A unit change in pain suffering scores at baseline was associated with a 0.2 percent increase in digit symbol test scores. The direction of this association did not change at follow-up. A unit change in pain suffering scores at follow-up was associated with a 0.3 percent change in digit symbol test scores. Although not significant, the positive association between pain suffering and DST scores seemed contrary to previous research.

A further examination of the total effects of pain suffering on DSYT scores at baseline showed the association to be negative. A unit change in the total effect (unmediated and mediated) of pain suffering was associated with one percent reduction in DSYT scores at baseline. The sum of unmediated and mediated effect of pain suffering

on DSYT scores at follow-up was positive. A unit change in the total effect of pain suffering at follow-up was associated with a 0.2 percent change in DSYT scores.

Two-Wave Paced Auditory Serial Addition Test Model

The association between pain suffering and PASAT scores was not significant at baseline ($p = 0.71$) and follow-up ($p = 0.21$). A unit increase in pain suffering scores at baseline was associated with a 0.4 percent reduction in PASAT scores at baseline. The direction of this association did not change at follow-up. A unit increase in pain suffering scores at follow-up was associated with a 0.8 percent reduction in PASAT scores at follow-up.

The magnitude of the total effect of pain suffering on PASAT scores was larger at baseline than at follow-up. A unit change in pain suffering scores at baseline resulted in mediated and unmediated effects that caused a 1.2 percent reduction in PASAT scores at baseline. The mediated and unmediated effects of pain suffering at follow-up caused a one percent reduction in PASAT scores at follow-up.

The non-significant association between pain suffering and cognitive test scores found in this study is contrary to evidence presented in the literature review. Brown et al. concluded that the association between pain and cognitive function was mediated by depressive symptoms.[342] On the other hand, some empiric evidence suggests that this may not always be the case.[343,344] Pain suffering is most commonly associated with impairments in information processing.[345] Although not significant, our study did find a negative association between pain suffering and PASAT scores, which is a measure of information processing. Alternatively, the addition of benzodiazepine dose as a control variable may have contributed to a finding that differed from previous literature. Other studies have failed to examine the association between depression, anxiety, and cognitive

[342] The relationship of pain and depression to cognitive function in rheumatoid arthritis patients. Brown SC, Glass JM, Park DC. *Pain*. 2002;96:279-284.
[343] Dick B, Eccleston C, Crombez G. Attentional functioning in fibromyalgia, rheumatoid arthritis, and musculoskeletal pain patients. *Arthritis and Rheumatism.* 2002;47:639
[344] Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis and Rheumatism*. 2001;44:2125-2133.
[345] Christensen H, Griffiths K, MacKinnon A, Jacomb P. A quantitative review of cognitive deficits in depression and Alzheimer-type dementia. *Journal of the International Neuropsychological Society.* 1997;3:631-651.

functioning in chronic pain patients while controlling for benzodiazepine dose. Thus, previous conclusions about the association between pain suffering and cognitive function may have been spurious in the absence of this control variable.

5.4.5 Association between Pain Behaviors, DST, DSYT, and PASAT

The final objective of the study was to determine the association between pain behaviors and cognitive function test.

Two-Wave Digit Span Test Model

There was a significant negative association ($p < 0.05$) between frequency of pain behaviors and digit span test scores. A unit increase in frequency of pain behaviors was associated with a 0.39 unit reduction in digit span test scores. The association between frequency of pain behaviors at follow-up and digit span test scores was positive ($\beta = 0.28$) and not significant ($p = 0.29$).

We next determined whether improvements in digit span test scores occurred across all levels of pain behaviors or only among those reporting the highest frequency of pain behaviors. A composite pain behavior variable at baseline and follow-up was created using the three indicators used to form the pain behavior construct. The composite was created by summing scores of individuals for frequency of pain behaviors at home, home or family related responsibilities, and pain continent down time. The sum of scores was divided by three.

The average total span scores at baseline and follow-up were plotted against the baseline and follow-up pain behavior composites (Figures 5.3 and 5.4). The plots clearly show that average span scores increased from baseline to follow-up across all pain behavior levels, supporting the conclusion that improvement in pain and reduction in pain behaviors was associated with an increase in digit span test scores.

Figure 5.3 Plot of Baseline & Follow-up Digit Span Test Scores by Pain Behavior Composite at Baseline

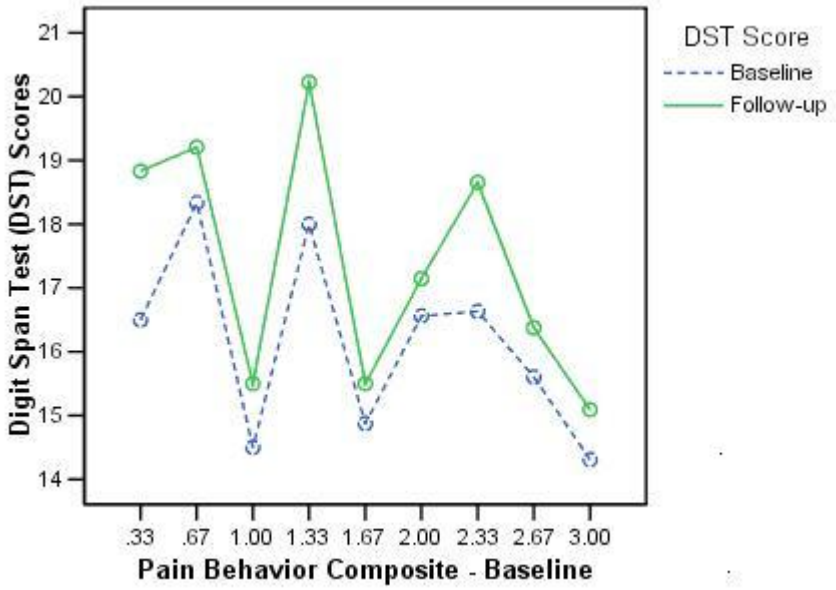
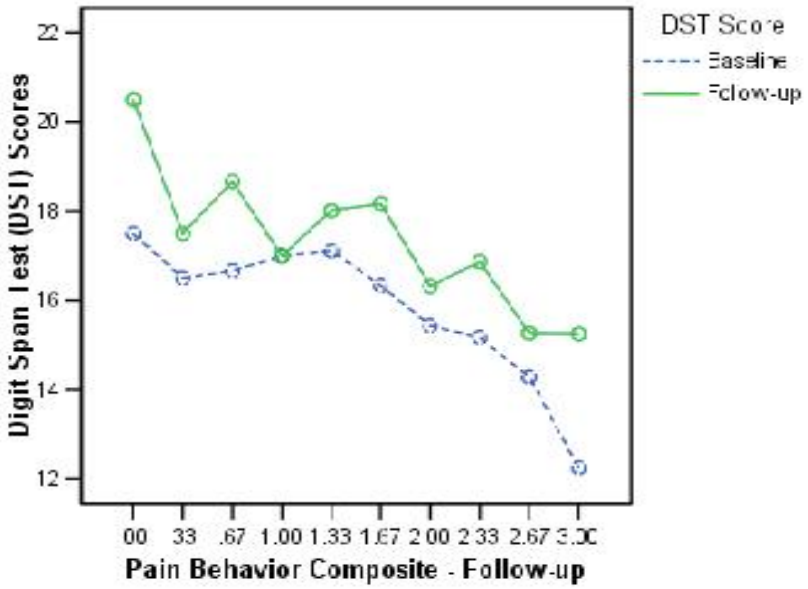


Figure 5.4 Plot of Baseline & Follow-up Digit Span Test Scores by Pain Behavior Composite at Follow-up



Two Wave Digit Symbol Test Model

The association between frequency of pain behaviors and digit symbol test scores at baseline and follow-up was negative and non-significant. The magnitude of these associations in comparison with associations examined between other variables seemed relatively large. A unit increase in frequency of pain behaviors was associated with a 13 percent reduction in digit symbol test scores. At follow-up, a unit increase in frequency of pain behaviors was associated with a three percent reduction in digit symbol test scores.

Similar to the procedure used above, digit symbol test scores at baseline and follow-up were plotted against pain behavior composites at baseline and follow-up. The plots can be viewed in figures 5.5 and 5.6, respectively. The plot shows a general negative association between the two variables. However, there was a lack of a consistent association between the two variables since patients with a pain behavior composite score in the range of 2.33 to 3 performed better on the DSYT than patients in the 1.67 to 1.99 range. This variability may account for the lack of a significant association between pain behaviors and DSYT scores. Patients who accounted for the most frequent pain behaviors at follow-up had marginally lower average scores on the test at follow-up. An improvement in test scores was observed across all other levels of pain behavior frequencies.

Figure 5.5 Plot of Baseline & Follow-up Digit Symbol Test Scores by Pain Behavior Composite at Baseline

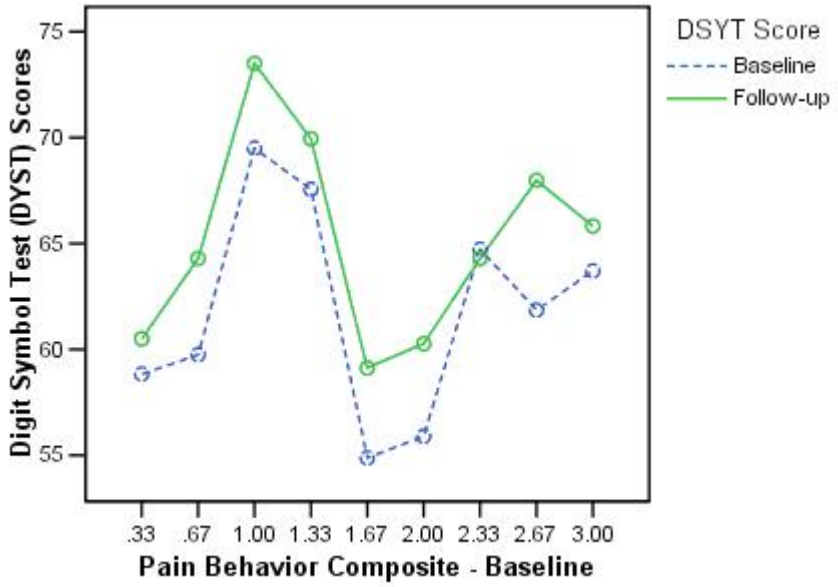
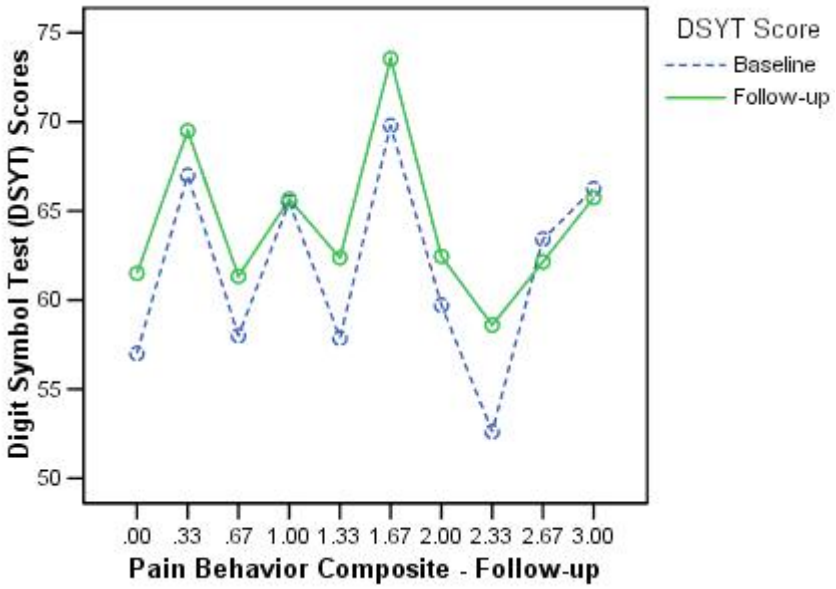


Figure 5.6 Plot of Baseline & Follow-up Digit Symbol Test Scores by Pain Behavior Composite at Follow-up



Two-Wave Paced Auditory Serial Addition Test Model

The association between frequency of pain behaviors and paced auditory serial addition test scores at baseline and follow-up was negative and non-significant. A unit increase in frequency of pain behaviors was associated with a 3.4 percent reduction in paced auditory serial addition test scores. At follow-up, a unit increase in frequency of pain behaviors was associated with a 2.2 percent reduction in paced auditory serial addition test scores.

Figure 5.5 and 5.6 present a plot of baseline and follow-up PASAT 2.4 scores by pain behavior composite at baseline and follow-up, respectively. Although the association between PASAT 2.4 scores and pain behavior composite at baseline tended to appear linearly negative, patients with pain behavior scores in the range of 2.33 to 2.67 had higher PASAT 2.4 scores than individuals with less frequent pain behaviors. A similar observation was made in the case of PASAT 2.0 scores (figure 5.7). These deviations may have contributed to the non-significant associations between PASAT scores and pain behaviors. However, the results show improvements in test scores across all levels of pain behaviors, which support the conclusion that improvement in pain and pain behaviors were associated with overall improvements in PASAT test scores.

Figure 5.7 Plot of Baseline & Follow-up PASAT 2.4 Scores by Pain Behavior Composite at Baseline

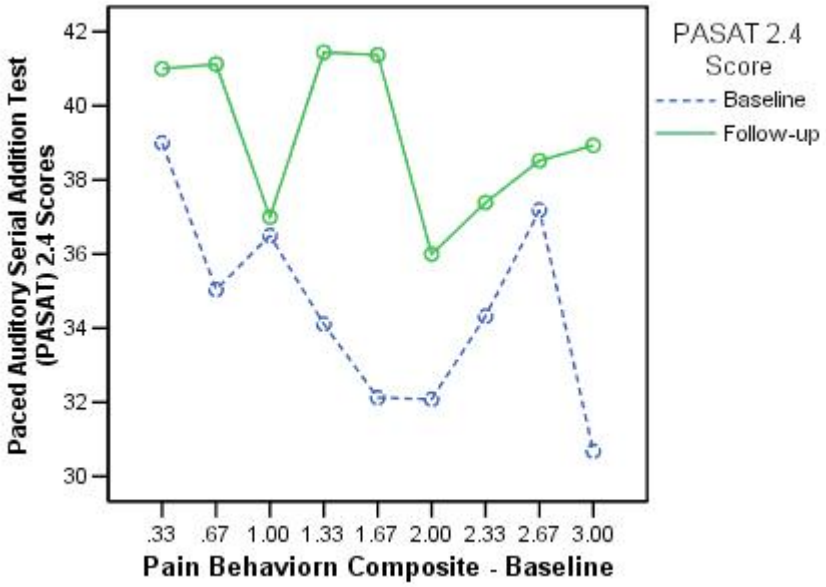


Figure 5.8 Plot of Baseline & Follow-up PASAT 2.0 Scores by Pain Behavior Composite at Follow-up

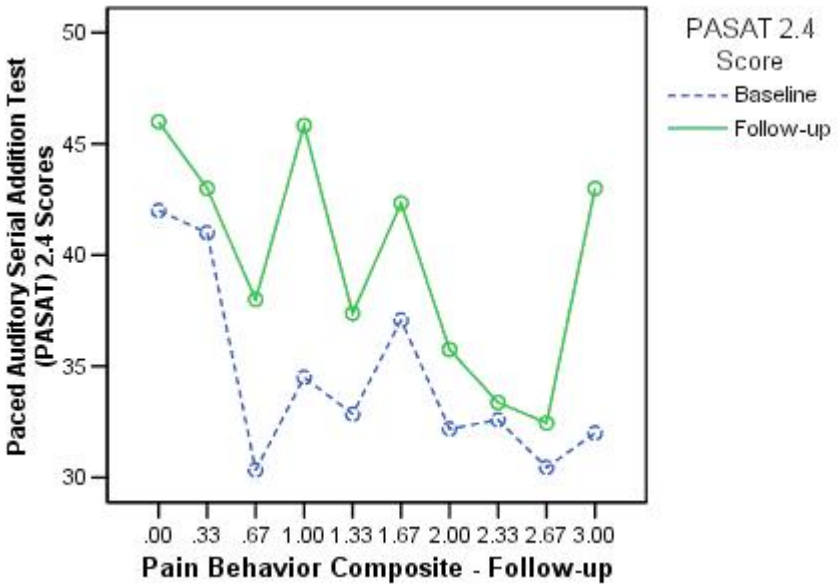


Figure 5.9 Plot of Baseline & Follow-up PASAT 2.0 Scores by Pain Behavior Composite at Baseline

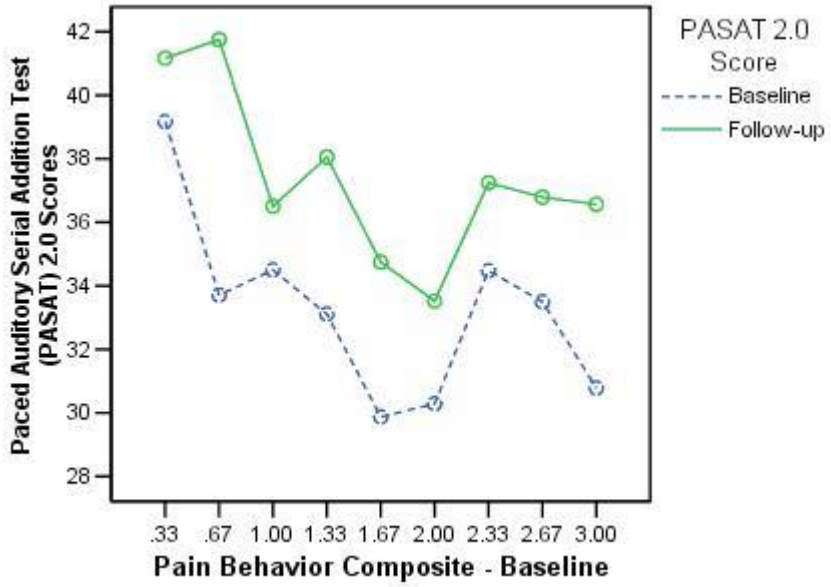
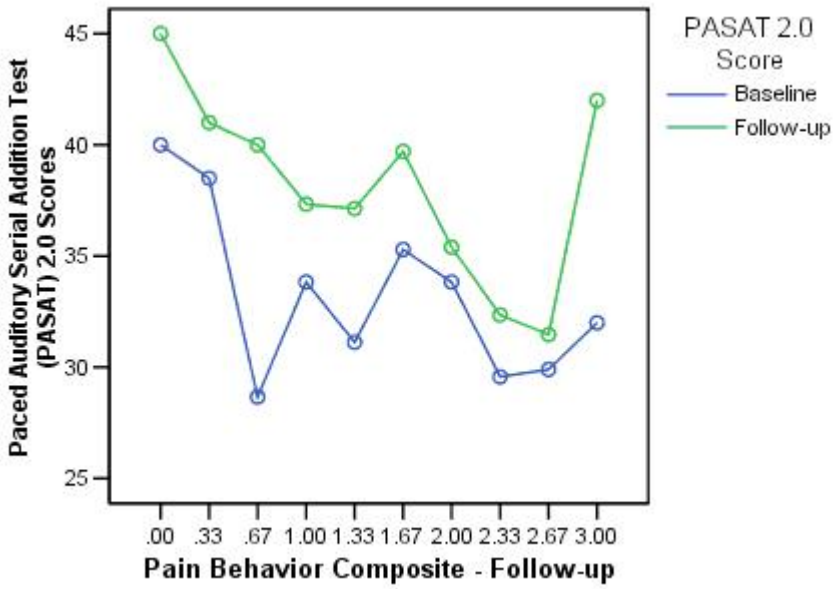


Figure 5.10 Plot of Baseline & Follow-up PASAT 2.0 Scores by Pain Behavior Composite at Follow-up



The above findings suggest that reduction in subjectively reported pain and pain behaviors were associated with some improvement in cognitive function test scores. Previous empirical work, which has shown an inverse association between the Arthritis Impact Measurement scale (AIMS) and cognitive function in fibromyalgia patients lends support to our findings.[346] AIMS is a measure of everyday dysfunction due to pain. Our study extends these findings by showing that interventions capable of reducing functional impairment also have positive effects on neuropsychological impairment.

These results also lend some credibility to the alternative specification of the SOPM model discussed above. Pain relief with Avinza may have influenced positive reinforcement in the ability of patients to obtain control over their pain. Control that can be sustained over prolonged periods may have reduced the associated threat with pain and reduced pain behaviors. Minimization of the threat could enable patients to refocus their cognitive resources, which led to a weakening of the association between pain behaviors and cognitive test scores.

The findings indicate that opioids, particularly long acting opioids must be an integral component of multidisciplinary pain management programs. Pain management models that ignore the utility of opioids may be able to achieve improved outcomes with the addition of controlled administration of sustained-release narcotic medications.

5.4.6 Association between Age, DST, DSYT, and PASAT

Two-Wave Digit Span Test Model

The results showed a negative association between age and digit span test scores at baseline, which approached significance (β = - 0.034, p = 0.06). At follow-up, this association was positive and not significant (β = 0.023, p = 0.33).

Two-Wave Digit Symbol Test Model

There was a significant negative association (p = 0. 03) between age and digit symbol test scores at baseline. A one year increase in age was associated with a 0.7 percent

[346] Park DC, Glass JM, Minear M, Crofford LJ. Cognitive function in fibromyalgia patients. *Arthritis and Rheumatism.* 2001;44:2125-2133.

decrease in DSYT scores. The magnitude of the association was weaker and not significant at follow-up. A one year increase in age was associated with a 0.3 percent decrease in DSYT scores (p = 0.15).

Two-Wave Paced Auditory Serial Addition Test

The association between age and PASAT scores at baseline and follow-up was negative and not significant. A one year increase in age was associated with a 0.2 percent reduction in PASAT scores at baseline and a 0.3 percent reduction in scores at follow-up.

5.4.7 Association between Gender and Pain Unpleasantness

On average, baseline pain unpleasantness ratings at the highest, lowest, and usual pain intensity levels for females was higher than males. The mean pain unpleasantness ratings provided by females at baseline were 13.04, 7.31, and 10.07 for highest, lowest and usual pain intensity levels respectively. The mean baseline ratings provided by males for these levels were 12.55, 5.66, and 9.22 respectively. Results from a cross-sectional study showed that women provided higher pain unpleasantness ratings than males except at the lowest pain intensity level.[347]

However, this trend was reversed at follow-up. The mean highest pain unpleasantness rating at follow-up was 11.17 for males and 10.93 for females. The mean lowest pain unpleasantness rating at follow-up was 4.30 for males and 3.83 for females. There was a very small difference in mean unpleasantness ratings at the usual pain intensity level between females (7.38) and males (7.16).

Results from the two-wave DST, DSYT, and PASAT models showed no significant difference in pain unpleasantness ratings between males and females. In an evaluation of two separate stages of pain models for males and females, Riley and colleagues showed that the association between pain unpleasantness and pain suffering was stronger among males.[348] Our sample was not large enough to generate these comparisons. Data from this study showed that women tended to report larger reductions

[347] Riley JL, Robinson ME, Wade JB, et al. Sex differences in negative emotional responses to chronic pain. *The Journal of Pain.*. 2001;2:354-359.
[348] Ibid.

in pain unpleasantness levels following treatment with sustained release morphine. This tendency of women to report extreme values at both ends of the scale deserves further study.

5.4.8 Association between Pain Suffering and Ethnicity

A majority of the sample (61.3%) was Caucasian. The two other relatively large ethnic groups who formed this sample were African Americans (20.2%) and Hispanics (9.7%). On average, the lowest levels of depression (mean = 7.31, sd = 4.4) and anxiety (mean = 7.74, sd = 4.2) at baseline were observed among Caucasians. All other ethnic groups had higher scores on both these indicators. The average score on the depression indicator was lower for African-Americans (9.68, sd = 4.6) than Hispanics (10.67, sd = 4.0). On average, African Americans reported higher anxiety levels (10.16, sd = 4.9) compared to Hispanics (9.13, sd = 4.6).

In order to determine variation in pain suffering ratings across ethnic groups, two groups were formed. One group included Caucasians and the second group included all other ethnic groups. Results from the hypothesized models showed that compared to other ethnic groups, Caucasians provided significantly ($p < 0.05$) lower pain suffering ratings at baseline. The magnitude of the difference in the case of the DST and PASAT models was 2.0, while the difference in the case of the DSYT model was 1.32. Although Caucasians had lower scores than other ethnic groups on the pain suffering construct at follow-up as well, the differences were not significant.

Data from this study were consistent with prior research which has shown that African-Americans and Hispanics tend to provide higher depression and anxiety ratings as compared to Caucasians.[349]

[349] Riley JL, Wade JB, Myers CD et al. Racial/ethnic differences in the experience of chronic pain. Pain. 2002;100:291-298.

5.5 Limitations

Researchers must strive to minimize the potential for bias in their studies. Despite the good intentions of the researcher, potential for bias cannot be eliminated. This study is no different and suffers from potential limitations.

The sample size for this study was small (n = 129), and patient attrition prevented us from utilizing all the data in modeling the relationships. Despite the small sample size, significant associations were found. However, significant associations between pain suffering and cognitive function test variables may have been elicited with a larger sample size. These data were originally to be analyzed using path analysis, and thus, sample size was calculated in a fashion used for a multiple regression analysis. Kline recommends that models analyzed using structural equation modeling include at least 5 subjects per parameter included in the model. Thus, with at least 50 parameters in this model, future studies contemplating a similar evaluation should intend to recruit 500 patients.

A convenience sampling procedure was used and only patients motivated to improve their condition may have enrolled in the study. Thus, patient self-selection may have biased the results in an upward direction. However, most patients enrolled in the study experienced chronic pain for a year or longer. The clinic specialized in interventional pain procedures and opioid pain management, and thus, in most cases represented a tertiary form of care for most patients.

Since patients completed the study forms in the presence of the researcher, the possibility that patients responded in a manner that they considered socially desirable cannot be excluded.

The assessment of patient behavior utilized one item requiring the judgment of the researcher/interviewer. The item lists several specific behaviors that must be rated. According to Polit and Hungler, observing patients in this manner is termed as a molecular approach to evaluation, wherein highly specific behaviors form the unit of observation. Thus, bias can be introduced into recording such behaviors by the researcher himself. Since only one individual made these judgments, inconsistencies in

interpreting certain behaviors were minimized. Additionally, this item was not incorporated as an indicator of the pain behavior factor for the present analysis.

Numerous issues were encountered with the scales. Three indicators of the original pain suffering scale: frustration, anxiety, and anger caused estimation problems with the follow-up data. It is likely that the problem was associated with the limited sample size.

Items assessing pain beliefs did not load on the pain suffering construct. As mentioned previously, the stages of pain model probably fails to capture real world phenomena without an adequate characterization of pain beliefs in the process.

The pain behaviors construct is dated and lacks sensitivity to change. In the case of the item assessing pain or family related responsibilities, patients with a raw score that exceeds seven are placed in a category characterized by the highest inability to perform previously discharged responsibilities. The scale lacks the ability to distinguish between a patient who is marginally impaired on a broad range of activities and a patient with significant impairments on a small set of activities. Both these patients could easily receive the same category score. Thus, the lack of scale sensitivity stems from the lack of consideration of the range of activities performed by patients.

Education has been associated with performance on tests of cognitive function. The current model did not control for the relative educational levels of participants.

Several patients underwent interventional procedures during the follow-up phase of the study. Procedures such as nerve blocks, facet joint injections, and steroid injections were administered to some study patients. These procedures when effective contribute significantly to pain relief and reduction in functional impairment. Exclusion of intervention effects may upwardly bias the treatment effect associated with Avinza.

However, improvement in symptoms and the consequent improvement in performance on neuropsychological tests were consistent with the study hypothesis that pain relief and associated improvement in behavioral and psychological symptoms contributes to improvement in cognitive function.

Improvement in cognitive function test scores may have been an artifact due to practice effects. Practice effects have been noted, particularly if successive tests are administered within a week from each other.[350] The one-month interval in assessments minimized this effect to a certain extent. The lack of a control group is an additional threat to internal validity. The true extent to which cognitive function improved cannot be determined without an adequate control group.

5.6 Conclusion

The sample for this study included chronic pain patients with a variety of diagnoses. The patients experienced significant disability secondary to pain. Addition of Avinza® to the short-acting narcotic medication regimen significantly improved subjectively reported outcomes of pain intensity. Patients utilizing short-acting narcotic analgesic medications reported high levels of pain intensity. Treatment and stabilization of patients with Avinza® resulted in reduction of average, maximum and minimum pain intensity levels. Reduction in pain intensity was associated with improvements in subjectively reported outcomes of pain unpleasantness, pain suffering, and pain behaviors.

The range of doses observed in the study indicates a large variance between individuals with respect to the extent of tolerance/sensitivity to narcotic medication dose. Achieving an optimal dose response varies across individual patients. The expertise and experience of pain management professionals are crucial to the achievement of a customized narcotic regimen for pain patients. A customized regimen minimizes the potential for adverse events, narcotic abuse, and the associated costs while improving patient outcomes.

Data from this study validated a four stage conceptualization of the pain process. The measurement model at baseline and follow-up were equivalent, which suggested reliability of the stages of pain model constructs measured at both waves.

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[350] Spreen O, Strauss E. A compendium of neuropsychological tests. Administration, norms, and commentary. Oxford University Press. New **York. 1998.**

Although statistical support for the stages of pain model in its current form was found, an alternate specification of the structural relationship may be plausible. The measurement component of the model may be improved by incorporating measures of self-efficacy measures in the model.

Frequency of pain behaviors at baseline were inversely associated with performance on cognitive function tests designed to measure short-term memory (digit span test), motor skills (digit symbol test), and information processing and attention (PASAT). Improvement in pain behaviors resulted in corresponding improvements in cognitive function test scores. This improvement was observed at all levels of pain behaviors. Thus, therapies targeted toward improving function in chronic pain patients may also contribute to improvements in short-term memory, motor skills, and information processing ability.

Benzodiazepine use was associated with impaired motor skills and information processing ability. Thus, treatment of anxiety with benzodiazepines should be reconsidered in chronic non-malignant pain populations.

Opioid therapy, particularly, long-acting morphine therapy (Avinza) does not contribute to cognitive impairment in chronic pain patients. Sustained release formulations of narcotics serve as one of several important tools for pain relief in a multidisciplinary pain management setting. In addition to pain relief, sustained release narcotics may contribute to improvements in neuropsychological functioning through mechanisms that enhance patient beliefs and reduce pain behaviors.

5.6 Future Research

The results from this study highlighted several deficiencies associated with the stages of pain model, particularly in the case of the pain beliefs construct. Prior research has shown that pain beliefs are predictive of numerous outcomes including depression and pain behaviors, thus the stages of pain model would be served better if the pain beliefs construct were evaluated with robust reliable and valid measures. The methodology to evaluate pain behaviors were strikingly different from those used to

assess other stages of pain items. Thus, an alternative means to assessing pain behaviors would also lead to improvements in the stages of pain model.

The analyses in the present study could have certainly improved with a sub-group analysis. Assessment of cognitive outcomes in sub-groups such as those formed with patients having varying levels of education, depression, or pain behaviors may allow providers to design targeted interventions for patients.

Appendix A

Tabulated Summary of Literature Examining the Efficacy and Safety of Opioid Therapy in Chronic Non-Malignant Pain

Author (Study Design)	*# of Participants*	*Diagnosis*	*Drug Treatment*	*Duration of trial*	*Efficacy*	*Adverse Effects*	*Comments*
Maier C et al. - 2002 Multicenter, prospective, randomized, double blind placebo-controlled cross over trial	Group 1 – 26, One dropped out prior to drug administration Group 2 –23	Neuropathic Pain - Post herpetic neuralgia (4) - Neuralgia (11) - Radiculopathy or myelopathy (12) - Other (6) Nociceptive Pain - LBP (12) - Other 93)	SR Morphine Placebo	2 weeks Group 1 – Morphine – week 1 Placebo – week 2 Group 2 – Reverse order	Intent-to-treat analysis no pain or good pain tolerance (morphine, n – 19) (Placebo, n - 3) Just bearable pain – (morphine, n – 17) (placebo, n – 16) 50% pain relief – Morphine (n – 16) Placebo (n – 1) 50% pain relief (NRS) Morphine (n – 20) Placebo (n – 1) Tolerability of pain Morphine (n – 36) Placebo (n – 17)	Tolerability of side effects Morphine (n – 38) Placebo (n – 41)	More patients with neuropathuc pain fulfilled criteria of full responders than patients with nociceptive pain
Attal N et al. - 2002. Randomized, double-blind placebo controlled crossover trial	N = 15	Post stroke pain (n= 9) Spinal cord injury (n=6)	IV Morphine 0.9% Saline Open label sustained release therapy after 4 weeks	Double blind phase – 4 weeks Open label trial - > 1 year	Average Pain reduction IV Morphine – 46.2% Saline – 24% 50% reduction in pain IV Morphine (n = 7) Saline (n = 2) Mean difference in pain after 4 weeks with oral therapy 20 mm (n = 8)	9 patients discontinued treatment due to adverse effects	Long-term opioid therapy was beneficial in a small proportion of patients Patients preferred treatment with the

[351] **Wilder-Smith CH, Hill L, Spargo K, Kalla A.. Treatment of severe pain from osteoarthritis with slow-release tramadol or dihydrocodeine in combination with NSAIDs: a randomized study comparing analgesia, antinociception and gastrointestinal effects. Pain. 2001;91:23-31.**

Allan L et al. – 2001. Multi-center, randomized, open-label crossover study to determine preference	MS Contin (average dose = 133.1 mg/day) (n = 92) Duragesic (average dose = 57.3 µg/hour) (n = 104) 196 of 256 patients completed trial	Chronic non-cancer pain (nociceptive and neuropathic)		Data were collected at day 7, 16, and 28 of each treatment period.	Average pain intensity ratings were significantly lower ($p < 0.001$) with fentanyl (57.8 cm, range – 33.1 to 82.5) than with SR morphine (62.9, range – 41.2 to 84.6)	Incidence of side-effects was similar in both groups, i.e., fentanyl (74%) and MS Contin (70%).	patch over oral opioid therapy. Good analgesic control with minimal side-effects were observed.
Wilder Smith CH et al[351]. – 2001 Open-label, randomized, parallel group study.	Dihydrocodeine slow release (n =29) Average dose day 28 = 130 mg Tramadol slow release (n =28) Average dose day 28 = 203 mg NSAIDs only (n = 30) Opioid groups also received concomitant NSAID medication and breakthrough pain medication.	Osteoarthritis	Dihydrocodeine 60mg (bid) Tramadol 100mg bid	One week observation followed by 4 weeks treatment with follow-ups.	Pain intensity at rest Significantly lower in tramadol group ($p < 0.04$) Pain Intensity during movement - No difference between groups, however pain intensity was lower at follow-up Quality of sleep and pain tolerance threshold at the arthritic joint improved in the opioid treatment groups	Constipation was a major side-effect	Improvement in pain and pain control was observed over 18 months and symptoms returned after drug withdrawal.
Roth SH et al. – Randomized, double-blind placebo controlled trial followed by an open-label study	CR Oxycodone (n = 44) 20 mg daily CR Oxycodone (n = 44) 40 mg daily	Osteoarthritis		Placebo controlled trial 14 days Open label trial Follow-up 6 months	Patients receiving the 40mg dose experienced significant improvements in pain intensity over the other groups. Improvements in sleep quality and mood were	29.5% patients withdrew from the treatment groups due to adverse effects.	Treatment with methadone

for six months. Taylor WF et al – 2000 Follow-up study two-years after initiation of treatment.	Placebo N = 59 Methadone On N = 19 Methadone Off N = 26 Lost to follow-up N = 19	 Chronic non-malignant pain		12 months 18 months Average duration – 18.6 months	observed at the end of 18 months 53% ON Methadone returned to work 23% OFF Methadone returned to work.	 12 patients in the OFF group discontinued therapy due to side-effects	provided relief, thereby allowing a subgroup of patients to return to work. Short-acting analgesics are associated with greater dysphoria Overall sleep quality improved on long acting therapy, worsened on placebo, and did not change with short-acting therapy.
Caldwell JR et al. – 1999 Open-label titration followed by a randomized, double blind, placebo controlled trial for 30-days.	Oxycontin 10mg bid (n = 34) Percocet (Oxycodone/APAP –5/325 mg) qid (n = 37) Pacebo (n = 36)	Osteoarthritis		Titration phase – 30 days Randomization phase	Percocet and Oxycontin produced comparable result for pain intensity. All three groups reported mean increase in pain intensity, Placebo (1.00, s.d.= 0.13) Oxycontin (0.44, s.d. = 0.13) Percocet (o.49, s.d. = 0.11)	53 patients withdrew from the study due to adverse effects (n =36) and poor pain control (n = 17)	Although patients experienced improvement in pain and mood, they did not report an increase in activities.
Jamison RN et al. – 1998. Randomized, open, long-term, repeated dose trial.	Randomization phase Naproxen – Maximum daily dose = 1000 mg Oxycodone Maximum daily dose =20mg Titrated dose Oxycodone + Sustained	Moderately severe back pain.		Randomization phase – 16 weeks All patients subsequently eligible for oxycodone and SR morphine and followed upto 16 weeks.	Average pain intensity ratings at 16 weeks on a 0-100 scale Naproxen - Increased by 1.2 Oxycodone – Decreased by 7.4 points Oxycodone + SR Morphine – Decreased by 15.9 Anxiety, depression, irritability were	Side effects occurred more frequently in the groups receiving opioid treatment.	

	release morphine Phase 2 – All patients eligible for the combination Maximum daily dose = 200mg				significantly lower for opioid groups compared to naproxen group.		Opioid analgesics may be effective in some neuropathic pain conditions.
Watson CPN, Babul N. - 1998 Randomized, double-blind crossover trial	N = 38 Oxycodone SR (10 mg) Placebo Patients permitted to take NSAIDs as usual.	Postherpetic neuralgia		4 weeks	Reports on average pain intensity measured by VAS and categorical rating scales were significantly lower in the opioid groups ($p < 0.001$). No significant differences were observed on BDI scores	Five participants withdrew while on opioids and three while on placebo due to side-effects.	Treatment with long-acting opiod therapy did not result in deterioration of performance on tests of cognitive function.
Haythornwaite et al. –1998. Open-label, long acting group vs usual care	Methadone/SR Morphine (n = 19) Short-acting opioids on a fixed-schedule (n = 10).	Chronic pain that persisted longer than six months.		Long-acting group – Mean = 5.8 months Short-acting group – Mean = 3.0 months.	Pain severity self-reported: Long-acting group Mean difference = - 1.93 Short-acting group Mean difference = -0.24. Patients on long-acting opioids reported lower levels of anxiety and hostility at follow-up. Performance on tests of cognitive function did not decline in the long-acting group and improved on the Digit Symbol test.	N/A	A subgroup of neuropathic pain patients can be effectively treated with long-acting narcotic analgesics.
Dellemjijn L et al. – 1998	Transdermal fentanyl	Non-cancer neuorpathic		12 week trial, followed by a	43.33% experienced greater than 50 percent relief in	Most commonly observed side-	

Open-label prospective study.	Morphine SR (60 mg) N = 48, 30 completed the trial	pain		washout period. Patients were ten permitted to continue on the drug. Final evaluation made at 2 years.	pain intensity, while the rest experienced less than 50 percent relief Proportion of patients with ≥ 50% pain relief was greater among those receiving fentanyl (65.4% and 50%) than among those receiving diazepam (15.4%) or saline (8.3%).	effects were: nausea, vomiting, pruritis, constipation. Addiction was not a problem	Long-acting opioid therapy may be effective in patients with neuropathic pain (without significant psychological comorbidity) who have not obtained benefit from other analgesic therapy.
Dellemijn PL & Vanneste JA. – 1997 Randomized double-blind active-placebo-controlled crossover trial.	Group 1 – Randomized to Fentanly (Average dose = 873 µg) or diazepam first (active placebo, average dose 52.1 mg) (n = 27) Group 2 - Randomized to Fentany (Average dose = 873 µg) or saline first	Nociceptive nerve pain, deaffrentation pain, and mixed neuropathic pain		One week titration phase. Patients were observed for 8 hours after infusions.	Pain intensity ratings were significantly lower in the group that received morphine first ($p < 0.02$). Patients that received placebo first were not responsive to either treatment.	Nausea, vomiting, dry mouth, light headedness, floating sensations, and itching were more commonly reported by patients receiving fentanyl.	Morphine reduced pain intensity, however no improvement in cognitive or functional status was observed.
Moulin DE et al. – 1996 Randomized double-blind crossover study.	SR morphine (Average dose = 83.5 mg) Benztropine (Active placebo) N = 61	Chronic persistent musculoskeletal pain (persistent pain ≥ 6 months)		Titration phase – 3 weeks Evaluation Phase – 6 weeks Washout phase Washout phase – 2 weeks	Overall mean pain intensity measured by VAS ($p = 0.0001$) and categorical scales ($p = 0.0001$) were significantly lower in the treatment group. Use of breakthrough medication was significantly greater in the placebo group ($p = 0.0001$).	Seven patients withdrew while on codeine and one on placebo due to side effects. Constipation, nausea, somnolence, and pruritis were more commonly observed in the treatment	Treatment with long-acting opioid therapy provides sustained pain relief evidenced by a reduction in use of breakthrough pain medication. Management of

						group.	neuropathic pain syndromes should not be excluded as a possibility.
Arkinstall et al. – 1995. Randomized, double-blind, placebo controlled crossover trial.	CR codeine (average dose = 273 mg) Placebo Acetaminophen + Codeine – 300/30 for breakthrough pain. (n = 46)	Chronic nonmalignant (rheumatic or back) pain		Patients were on either codeine or placebo for a week and then crossed over to corresponding treatment.	Response measured by 100mm VAS Greater than 70 mm reduction in pain – 54.54% <70mm and >30mm pain relief at two or more assessment times – 18.18% < 30mm pain relief and intolerable side effects – 22.72%	Side-effects observed included nausea, vomiting, sweating, itching, and lack of concentration,	Neuropathic pain and comorbidities such as depression, abuse, and addiction were associated with a poor response.
McQuay HJ et al. – 1992. Open-label, patient controlled analgesia trial	IV Morphine N = 22	Chronic non-malignant and cancer pain.		24 hours	Pain relief: Complete – 34% Partial – 46% No relief – 20%	24% became addicted. 22% developed tolerance to opioid analgesia,	Bothtypes of pain (nociceptive and neuropathic) were responsive to opioid treatment.
Bouckoms AJ et al. – 1992. Retrospective review.	Oxycodone derivatives, codeine, meperidine, methadone N = 59	Nociceptive and neuropathic pain.		Average duration of treatment with narcotic analgesics – 36 months.	Superior response was observed with the higher dose of morphine. Side effect frequency was greater with the lower dose of morphine.	Common side effects were drowsiness, itchiness, and concentration difficulties.	Treatment of pain with opioids should be considered as a last line of therapy.
Jadad AR et al. – 1992 Randomized double-blind crossover patient controlled analgesia study	IV Morphine Doses: 10mg/ml 30mg/ml Average dose = 230 mg 10 of 13 patients completed the 2 study phases	Nociceptive and neuropathic pain.		Eight hours	88.5%of patients achieved adequate pain control	Constipation and edema were most commonly observed	Long-term opioid therapy in CNMP patients is safe and effective.
Tennant F et al. – 1988.	oxycodone, methadone,	Chronic nociceptive		Patients were on narcotic	Adequate but incomplete pain relief without	Most common side-effects were	Long-term opioid therapy was associated with

Open-label trial	codeine, propoxyphene, hydromorphone, meperidine, and hydrocodone Variable doses n = 52	and neuropathic pain.		analgesic therapy for varying lengths of time.	substantial improvement in functional status	constipation and edema of the extremities.	reduction in pain and disability.
Portenoy RK, Foley KM. – 1986. Retrospective evaluation.	Methadone, levorphanol, oxycodone, propoxyphene, meperidine, codeine, pentazocine, N = 38	Intractable, non-malignant pain patients.		Patients were included in the review if they had received opioid therapy for 6 or more months.	29% of patients reported adequate relief (n =11) 34 % of patients reported partial relief (n =13). 37 % of patients reported episodic sever pain (n = 14)	Abuse and diversion became apparent in two cases. No other significant side-effects were reported by patients.	Fentanly use in chronic pain was associated with very minor improvements in quality of life dimensions (physical, mental, and social).
Schofferman, 1999. Open label opioid trial	Various narcotic analgesics N = 33,	Chronic low back pain		6-12 weeks initial treatment; long-term follow-up in patients with improvement. Avg. Follow-up duration was 32 months	Pain scores and disability scores improved by 3.6 and 13.8 points measured on a 10 and 100 point scale respectively (n =21). Seven patients did not respond to therapy.	Five patients discontinued trial due to intolerable side-effects. Specific side-effects were not reported.	
Milligan et al. – 2001 Open label trial	Average fentanyl dose = 90 µg/hour at the end of the study 301/532 patients completed the study.	Chronic non-malignant pain patients with moderate response to other opiodis.		Final follow-up assessments were made 12 months after baseline.	On average, patients reported pain to have improved from severe/very severe to moderate.	Frequently reported side-effects include: nausea, constipation, and somnolence. Respiratory depression, drug abuse/dependence, and withdrawal were rarely observed.	

Appendix B

Chronic Pain Study

Dear Patient,

Chronic pain affects a significant part of society. Often, patients do not find relief from pain despite attempting treatment with several pain management strategies. Pain medications form an integral part of the treatment of chronic pain. Although pain may originate from biological sources, psychological and social factors also constitute the pain process.

We, Ravi Panjabi, MD (Advanced Pain Management Group Inc.), Sumeet Punjabi, B. Pharmacy, MS and Marvin Shepherd Ph.D. (University of Texas at Austin) are currently conducting a research project to examine the effects of pain medications. The project involves the completion of several forms and paper-based tests to measure attention and ability to process information. None of these tests are intended to be stressful, nor will they in any way influence your treatment. You will not be asked to take any special medications or undergo any special treatments other than what your physician recommends for the treatment of your pain condition.

Your participation in this study is voluntary. Your decision to either participate or decline participation in this project will in no way influence the level of care that you shall receive at Advance Pain Management Group Inc.

Participation will require approximately one hour of your time on two separate occasions. As a recognition of your time and willingness to participate in the study, you will receive a coupon for your medications (subject to change).

Thank you for your assistance.

Sincerely,

Sumeet Punjabi M.S.
Doctoral Candidate
Pharmacy Administration Division
College of Pharmacy
University of Texas at Austin

Marv Shepherd Ph.D.
Director
Pharmacy Administration Division
College of Pharmacy
University of Texas at Austin

Ravi Panjabi M.D.
Physician & Director
Advanced Pain Mangement Group Inc.
Castro Valley, CA

Appendix C

IRB# _____

Informed Consent to Participate in Research

The University of Texas at Austin

You are being asked to participate in a research study. This form provides you with information about the study. The Principal Investigator (the person in charge of this research) or his/her representative will also describe this study to you and answer all of your questions. Please read the information below and ask questions about anything you don't understand before deciding whether or not to take part. Your participation is entirely voluntary and you can refuse to participate without penalty or loss of benefits to which you are otherwise entitled.

Title of Research Study:

Cognitive Function in Chronic Non-Malignant Pain Patients Treated with Long-Acting Narcotic Analgesics

Principal Investigator(s) (include faculty sponsor), UT affiliation, and Telephone Number(s):

Sumeet Punjabi, M.S.
Graduate Student/Doctoral Candidate
512-417-8006

Marv Shepherd, Ph.D.
Professor/ Director, Center for Pharmacoeconomic Studies
512-471-8762

Ravi Panjabi, M.D.
Physician-in charge
Advanced Pain Management and Rehab Group, Inc
510-461-0482

Funding source:

This study is not funded

What is the purpose of this study?

You are being asked to participate in this study because your physician has decided to switch your therapy from short-acting narcotic analgesic medications to long-acting narcotic analgesic medications. The purpose of this study is to evaluate the effects of this switch on your pain, emotional status, usual activities, and attention.

What will be done if you take part in this research study?

If you decide to take part in the study, we will ask you to complete several forms that are intended to examine various aspects of your pain condition. The following aspects of your condition will be assessed on two separate occasions:

- Severity of pain
- Negative emotions due to pain
- Negative beliefs about pain
- Interference in activities due to pain
- Beck Depression Inventory – a screening tool designed to assess depression
- Dose of narcotic analgesic and benzodiazepine
- Medical chart information to assess duration of pain, type of pain, location of pain, and other relevant information
- Performance on three measures of attention

A portion of the interview may be taped to ensure accurate transcription of the information you provide. Completion of these forms may require 45 to 60 minutes of your time on two occasions about one month apart. In addition, you will be required to come into the clinic each week for the three intermittent weeks in order for us to monitor your progress. Based on these progress assessments, dosage of the long-acting narcotic analgesic may be modified to achieve better pain control or minimize side-effects.

You will be asked to complete the following three tests intended to assess your attention: digit span backwards and forwards test; digit symbol test; and the paced auditory serial addition test. These assessments will evaluate your attention by asking you to complete some exercises using numbers and symbols on two occasions. The total time to complete these tests for each visit will be approximately 20 minutes.

What are the possible discomforts and risks?

The study poses minimal risk to you as a patient. Most of the forms are straightforward and easy to complete. One test, i.e., the PASAT is a little difficult and intensive. The purpose of the test is not to evaluate your knowledge, but ability to concentrate due to your chronic pain condition.

Some side-effects associated with the use of long-acting narcotic analgesics include: constipation, nausea, vomiting, sweating, itching, and somnolence. It is recommended that alcohol not be consumed while using these narcotic analgesics. In addition, these agents may produce sedative effects, and thus you should limit activities that involve driving or operating heavy machinery.

Although the utmost precautions will be taken to maintain confidentiality, loss of confidentiality is a potential risk that you should be aware of. A detailed description of the measures that will be taken to minimize this possibility is provided below.

What are the possible benefits to you or to others?

- One benefit of participating in the study is the routine follow-up visits that would enable optimal dosage titrations of the long-acting narcotic analgesic. Side-effects associated with the use of long-acting narcotics will be addressed sooner as you will be required to visit the clinic every week for four weeks as opposed to usual care where patients visit the clinic once every two weeks in a four week period.
- Results from this study may provide health providers with information about the potential benefits of using long-acting opiate pain medications.

If you choose to take part in this study, will it cost you anything?

Your choice to participate in this study will not present any additional financial burden on you. Any charges that you incur would be those that would be billed to you by the clinic for routine treatment and would be the same if you did not participate in this study. Your insurance company will be billed for the two extra visits due to the study; however, you will not receive copay charges for these extra visits. You will bear no financial responsibility for these extra visits.

Will you receive compensation for your participation in this study?
What if you are injured because of the study?

You will not receive any compensation for participation in this study. The study does not pose any "known" physical risk or harm to you as a patient. Discomfort or side-effects due to medications will be treated as usual by physician-in-charge. Your insurance will be

charged for the provision of such care. No payment can be provided in the event of a medical problem.
Continuing medical care and/or hospitalization for research-related injuries will not be provided free of charge nor will financial compensation be available either from the physician-in-charge, researchers, or the University of Texas at Austin.

If you do not want to take part in this study, what other options are available to you?
Participation in this study is entirely voluntary. You are free to refuse to be in the study, and your refusal will not influence current or future relationships with The University of Texas at Austin. You are free to refuse to participate in the study or withdraw from the study at any time. Your decision to not participate or withdraw from the study will not influence the medical care you receive at Advanced Pain Management and Rehab Group Inc or with your current physician.
In addition to treatment with long-acting narcotic therapy, your physician will advise you of alternative treatments for pain relief such as injections (epidural and nerve blocks), prosthetic devices, transcutaneous electrical nerve stimulation, H-wave therapy, physical therapy, acupuncture, and massage.

How can you withdraw from this research study and who should I call if I have questions?

If you wish to stop your participation in this research study for any reason, you should contact: Sumeet Punjabi at (512) 417 8006 or Dr. Ravi Panjabi at (510) 461 0482. You are free to withdraw your consent and stop participation in this research study at any time without penalty or loss of benefits for which you may be entitled. Throughout the study, the researchers will notify you of new information that may become available and that might affect your decision to remain in the study.

In addition, if you have questions about your rights as a research participant, please contact Clarke A. Burnham, Ph.D., Chair, and the University of Texas at Austin Institutional Review Board for the Protection of Human Subjects, 512/232-4383.

How will your privacy and the confidentiality of your research records be protected?

Everything we learn about you in the study will be confidential and your information will be maintained private. All the information you give us including audio tapes with voice recordings will be kept locked in your physician's office.

Your medical chart will be reviewed to obtain information on birth date, medical record number, medications, diagnosis, type of pain, duration of pain and prior surgery. Access to this information will be limited to the researchers and the charts will never

leave the clinic. Any information transcribed from the medical charts will be coded and information that can be used to identify you removed so as to protect patient identity. The charts shall in all circumstances be maintained under the control of Advanced Pain Management and Rehab Group, Inc.

A voice recorder will be used to facilitate data transcription. While at the clinic collecting data, all tapes will be maintained in a locked filing cabinet. The use of the tapes is to ensure that the information obtained from your tests is recorded correctly. The tapes will be maintained until the end of the study and subsequently erased.

All data will be coded at the clinic. The data will be coded without any patient identifiers (name, medical record number, date of birth) using only the study identification number assigned to each patient to link coded data with chart information. Patient names, addresses, and other patient identifiers will be deleted from the file. Specific detailed dates, such as day, month, and year of birth will be converted to only the year. Thus, any data that leaves the clinic will be de-identified. Any data or information brought to the University of Texas at Austin will be in a de-identified fashion. All the results from this study will be presented in an aggregated form that would prevent your identification. At the University of Texas, the researcher and the researcher's major professor are the only people who will have access to the data.

Authorized persons from The University of Texas at Austin and the Institutional Review Board have the legal right to review your research records and will protect the confidentiality of those records to the extent permitted by law. If the research project is sponsored then the sponsor also has the legal right to review your research records. Otherwise, your research records will not be released without your consent unless required by law or a court order.

If the results of this research are published or presented at scientific meetings, your identity will not be disclosed.

Will the researchers benefit from your participation in this *study ?*

The researchers will not obtain any monetary benefit from your participation in the study.

Signatures:

As a representative of this study, I have explained the purpose, the procedures, the benefits, and the risks that are involved in this research study:

_____ _____

Signature and printed name of person obtaining consent Date

You have been informed about this study's purpose, procedures, possible benefits and risks, and you have received a copy of this Form. You have been given the opportunity to ask questions before you sign, and you have been told that you can ask other questions at any time. You voluntarily agree to participate in this study. By signing this form, you are not waiving any of your legal rights.

_____

Printed Name of Subject Date

_____

Signature of Subject Date

_____

Signature of Principal Investigator Date

Appendix D

Instrument at Baseline and Follow-up

Background Information

Today's Date: _____

Medical Record Number* _____ Study ID #_____

Birth Date* _____ Gender ___Male
___Female

Ethnicity

_____ Caucasian _____African-American

_____Hispanic/Latin American _____American Indian

_____Asian _____Other, Please Specify: _____

Average Daily _____ (short-acting narcotic analgesic) Dose^

Average Daily _____ (benzodiazepine) Dose^

Duration of Pain _____

Other Medications* _____

_____

Diagnosis* _____

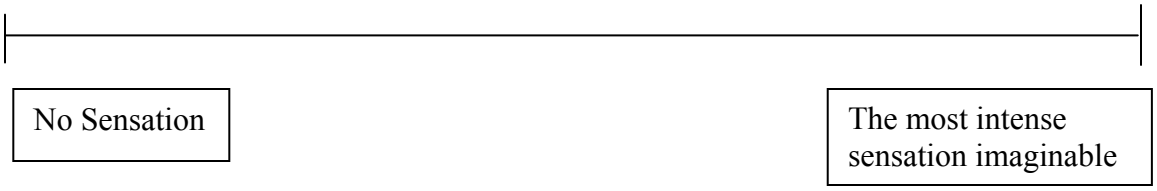
Type of Pain* ____Nociceptive ____Neuropathic ____Mixed

Prior Surgery* ____Yes ____No

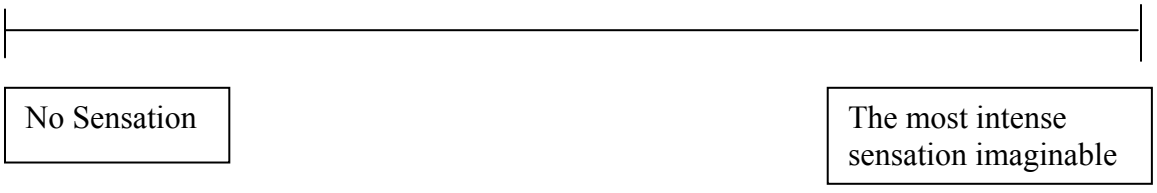
Pain Intensity VAS

Indicate along the scale below the intensity of the painful sensation at its **highest intensity** during the past week.

Indicate along the scale below the intensity of the painful sensation at its **lowest intensity** during the past week.



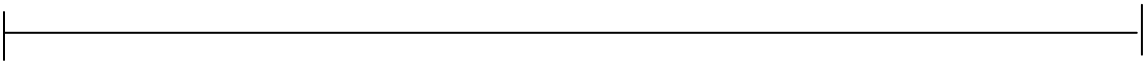
Indicate along the scale below the intensity of the painful sensation at its **usual intensity** during the past week.



Pain Unpleasantness VAS

"There are two aspects of pain which we are interested in measuring: the intensity, how strong the pain feels, and the unpleasantness, how unpleasant or disturbing the pain is for you. The distinction between these two aspects of pain might be made clearer if you think of listening to a sound, such as a radio. As the volume of the sound increases, I can ask you how loud it sounds or how unpleasant it is to hear it. The intensity of pain is like loudness; the unpleasantness of pain depends not only on intensity but also on other factors which may affect you.[352]"

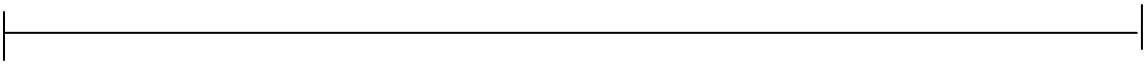
Indicate along the scale below how unpleasant or disturbing your pain was when it was at its **highest intensity** during the past week.



Not bad at all

The most intense bad feeling

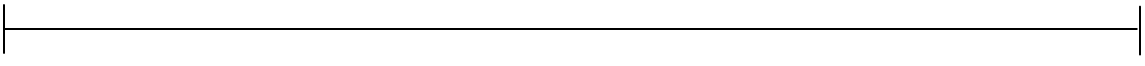
Indicate along the scale below how unpleasant or disturbing your pain was when it was at its **lowest intensity** during the past week.



Not bad at all

The most intense bad feeling

Indicate along the scale below how unpleasant or disturbing your pain when it was at its **usual intensity** during the past week.



Not bad at all

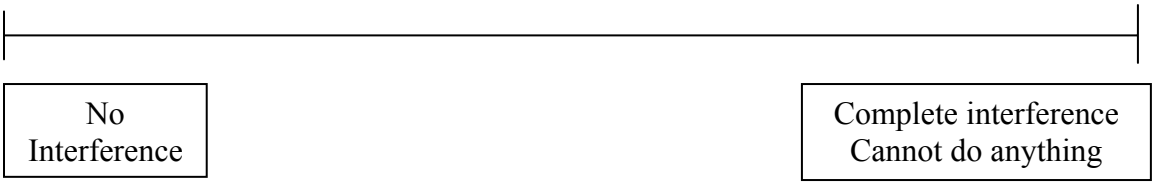
The most intense bad feeling

[352] Price DD, McGrath PA Rafii A, Buckinham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain.*. 1983;17:45-56.

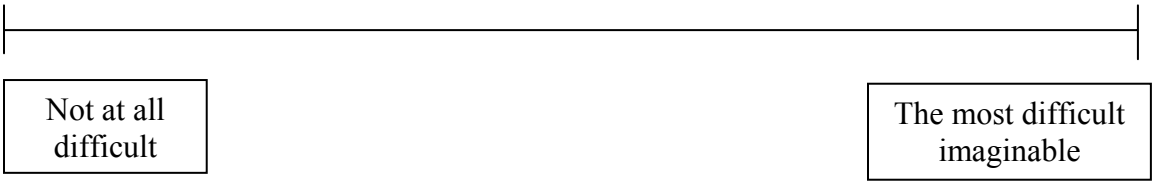
Pain Beliefs

For each of the following, indicate the extent by making a mark along the appropriate scale. The further to the right, the greater the extent.

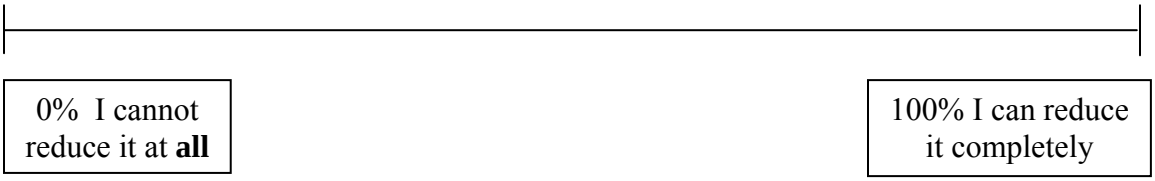
1. How much does your pain prevent your from doing what you want to do?



2. How difficult is it to endure the pain over time?



3. In general, how much can you reduce the intensity of your pain if you want



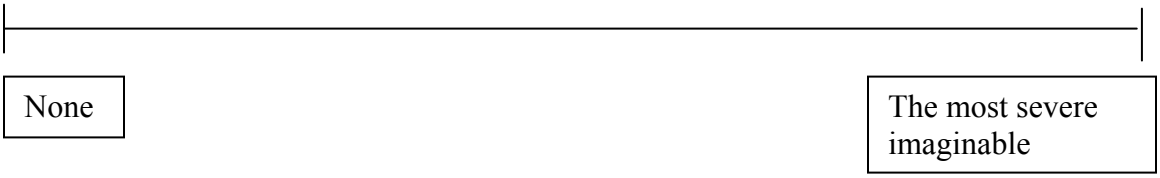
4. In general, how likely do you feel that your pain will be removed or cured?

Pain Suffering

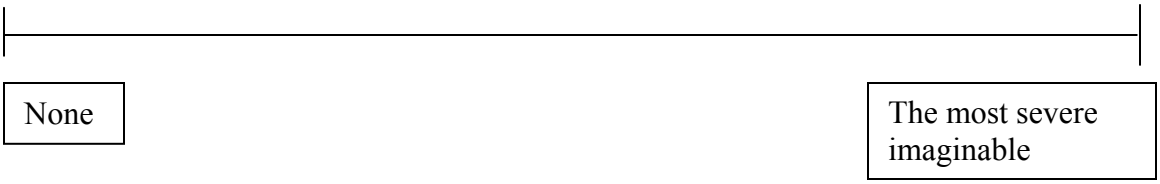
What kind of negative feelings accompany your pain? Check along each scale below the intensity of each feeling as it has related to your pain over the past week.

1. Depression

2. Anxiety



3. Frustration



4. Anger

5. Fear

☐

Pain Behaviors

Items from the Psychological Pain Inventory Assessing Pain Behaviors

Ask specifically: "When you are at home and the pain is really bad, how can your family tell that you hurt that way?" Ask about all pain behaviors that are not mentioned spontaneously. Also ask how often the pain is bad enough that the patient ends up doing each of the pain behaviors he engages in. Check each pain behavior which occurs with the frequency indicated. Patients who live alone will be assigned a "0."

- ❑ Hold or grasp the area that hurts, 3 times a day or more =1
- ❑ Wince or cringe, 3 times a day or more =2
- ❑ Call a doctor, once a month or more = 3
- ❑ Cry, once a week or more = 3
- ❑ Moan, once a week or more = 3
- ❑ Say it hurts, once a day or more. Ask how this is done, and specify whether it is done with
    - ❑ no affect = 1
    - ❑ some affect = 2
    - ❑ much affect = 3
- ❑ Pace, three times a week or more = 2
- ❑ Go into another room by self, 3 times a week or more = 2
- ❑ Lie down more than once a day = 2

  If this happens at work too with any frequency = 3
- ❑ Sit down, more than 3 times per day = 1
- ❑ Change position frequently = 0
- ❑ Scream, if at all = 3
- ❑ Take medications = 0 (unless addicted; then =3)
- ❑ Ask for help with things that patient would normally be able to do himself/herself, once a day or more = 3
- ❑ Gets angry or irritable, 3 times per week or more = 2
- ❑ Other (specify): _____

Ask in relation to the pain behaviors considered generally: "When family members see you doing these things, and hurting especially badly, how do they respond to you?" Again, ask about any response that is not mentioned spontaneously, determine the general frequency with which each response occurs, and check each response that occurs with the frequency indicated.

- ❑ Express sympathy verbally, daily or almost everyday = 2
- ❑ Withdraws from patient, daily or almost everyday = 0 (unless MMPI-SI 60; then = 2)
- ❑ Encourages patient to take remedial action (i.e., to take meds, lie down, apply heating pad, call doctor, etc.) daily or almost every day = 1
- ❑ Helps patient take remedial action (i.e., gets the meds or heating pad, draws bath, calls doctor, etc) daily or almost everyday = 2
- ❑ Actually administers remedial medication (i.e., gives back rub, holds patient, gives injection, etc.) daily or almost every day = 3
- ❑ Offers to do whatever work the patient is either attempting to do or scheduled to do, when this is something the patient usually feels capable of doing, daily or almost every day = 3
- ❑ Complains = 0
- ❑ Does nothing (ignores patient) = 0
- ❑ Other (specify): _____

Use the following checklist to indicate what home or family related responsibilities the patient discharged prior to the pain problem as compared to now. Under "*Before*" check only those activities that the patient did at least half of the time before (i.e., it must have been primarily the patient's responsibility – not mostly someone else's in the family). Check under "*Less now*" if, due to the pain, the frequency with which the patient does the activity has decreased but by no more than 50 percent. Check under "*Never now*" if the frequency has decreased by more than 50 percent.

Responsibility	Before	Less Now	Never Now
Housecleaning	_____	_____	_____
Clothes washing	_____	_____	_____
Clothes ironing	_____	_____	_____
Shopping	_____	_____	_____
Cooking	_____	_____	_____
Repair work (home)	_____	_____	_____
Repair work (car)	_____	_____	_____
Yard work	_____	_____	_____
Errands	_____	_____	_____
Caring for children	_____	_____	_____
Disciplining children	_____	_____	_____
Driving other family members	_____	_____	_____
Family finances	_____	_____	_____
Family correspondence	_____	_____	_____
Other (specify):			
_____	_____	_____	_____
_____	_____	_____	_____
_____	_____	_____	_____

Determine about how many daytime hours are spent lying down because of pain these days?
No more than one hour per day = 0
Greater than one but less than two hours per day = 1
Two to four hours per day = 2
More than four hours per day = 3 (Specify how many): _____

Describe the patient's pain behavior that you observed in the interview:

- ❑ Held or grasped the area that hurt = 1
- ❑ Winced or cringed = 2
- ❑ Moaned = 3
- ❑ Paced = 3
- ❑ Changed position frequently = 1
- ❑ Took medications = 3
- ❑ Became irritable = 2
- ❑ Asked to stop interview = 3

- ❑ Said it hurt, not in direct response to a question or statement by the interview, with
  - ❑ much affect = 3
  - ❑ some affect = 2
  - ❑ little affect = 2
  - ❑ no affect = 1

- ❑ Asked to call doctor = 3
- ❑ No pain behavior was observed = 3 (0 if patient is currently getting very much or total relief from treatment).

Appendix E

Beck Depression Inventory

Choose one statement from among the group of four statements in each question that best describes how you have been feeling during the past few days. Circle the number beside your choice.

1	0 I do not feel sad. 1 I feel sad. 2 I am sad all the time and I can't snap out of it. 3 I am so sad or unhappy that I can't stand it.	7	0 I don't feel disappointed in myself. 1 I am disappointed in myself. 2 I am disgusted with myself. 3 I hate myself.
2.	0 I am not particularly discouraged about the future. 1 I feel discouraged about the future. 2 I feel I have nothing to look forward to. 3 I feel that the future is hopeless and that things cannot improve.	8.	0 I don't feel I am any worse than anybody else. 1 I am critical of myself for my weaknesses or mistakes. 2 I blame myself all the time for my faults. 3 I blame myself for everything bad that happens.
3	0 I do not feel like a failure. 1 I feel I have failed more than the average person. 2 As I look back on my life, all I can see is a lot of failure. 3 I feel I am a complete failure as a person.	9	0 I don't have any thoughts of killing myself. 1 I have thoughts of killing myself, but I would not carry them out. 2 I would like to kill myself. 3 I would kill myself if I had the chance.
4	0 I get as much satisfaction out of things as I used to. 1 I don't enjoy things the way I used to. 2 I don't get any real satisfaction out of anything anymore. 3 I am dissatisfied or bored with everything.	10	0 I don't cry any more than usual. 1 I cry more now than I used to. 2 I cry all the time now. 3 I used to be able to cry, but now I can't cry even though I want to.
5	0 I don't feel particularly guilty. 1 I feel guilty a good part of the time. 2 I feel quite guilty most of the time. 3 I feel guilty all of the time.	11	0 I am no more irritated by things than I ever am. 1 I am slightly more irritated now than usual. 2 I am quite annoyed or irritated a good deal of the time. 3 I feel irritated all the time now.
6	0 I don't feel I am being punished. 1 I feel I may be punished. 2 I expect to be punished. 3 I feel I am being punished.	12	0 I have not lost interest in other people. 1 I am less interested in other people than I used to be. 2 I have lost most of my interest in other people. 3 I have lost all of my interest in other people.

13	0 I make decisions about as well as I ever could. 1 I put off making decisions more than I used to. 2 I have greater difficulty in making decisions than before. 3 I can't make decisions at all anymore.	18	0 My appetite is no worse than usual. 1 My appetite is not as good as it used to be. 2 My appetite is much worse now. 3 I have no appetite at all anymore.
14	0 I don't feel that I look any worse than I used to. 1 I am worried that I am looking old or unattractive. 2 I feel that there are permanent changes in my appearance that make me look unattractive. 3 I believe that I look ugly.	19	0 I haven't lost much weight, if any, lately. 1 I have lost more than five pounds. 2 I have lost more than ten pounds. 3 I have lost more than fifteen pounds. (Score 0 if you have been purposely trying to lose weight.)
15	. 0 I can work about as well as before. 1 It takes an extra effort to get started at doing something. 2 I have to push myself very hard to do anything. 3 I can't do any work at all.	20	0 I am no more worried about my health than usual. 1 I am worried about physical problems such as aches and pains, or upset stomach, or constipation. 2 I am very worried about physical problems, and it's hard to think of much else. 3 I am so worried about my physical problems that I cannot think about anything else.
16	. 0 I can sleep as well as usual. 1 I don't sleep as well as I used to. 2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep. 3 I wake up several hours earlier than I used to and cannot get back to sleep	21	0 I have not noticed any recent change in my interest in sex. 1 I am less interested in sex than I used to be. 2 I am much less interested in sex now. 3 I have lost interested in sex completely.
17	0 I don't get more tired than usual. 1 I get tired more easily than I used to. 2 I get tired from doing almost anything. 3 I am too tired to do anything		

SCORING

1 – 10: These ups and downs are considered normal.
11 – 16: Mild mood disturbance
17 – 20: Borderline clinical depression
21 – 30: Moderate depression
31 – 40: Severe depression
over 40: Extreme depression

Appendix F

Follow-up Dose Assessments

Today's Date: _____

Medical Record Number* _____ Study ID #_____

Average Daily _____ (long-acting narcotic) Dose in previous week^

Average Daily _____ (breakthrough analgesic) Dose in previous week^

Average Daily _____ (benzodiazepine) Dose in previous week^

* Information will be obtained from patient chart
^ Information will be obtained from patient

Appendix G

Digit Span Test

Discontinue Rule

Digits Forward & Backward

Score of 0 on both trials of any item

For both Digits Forward & Backward, administer both trials of each item even if Trial 1 is passed. Administer Digits Backward even of examinee scores 0 on Digits Forward

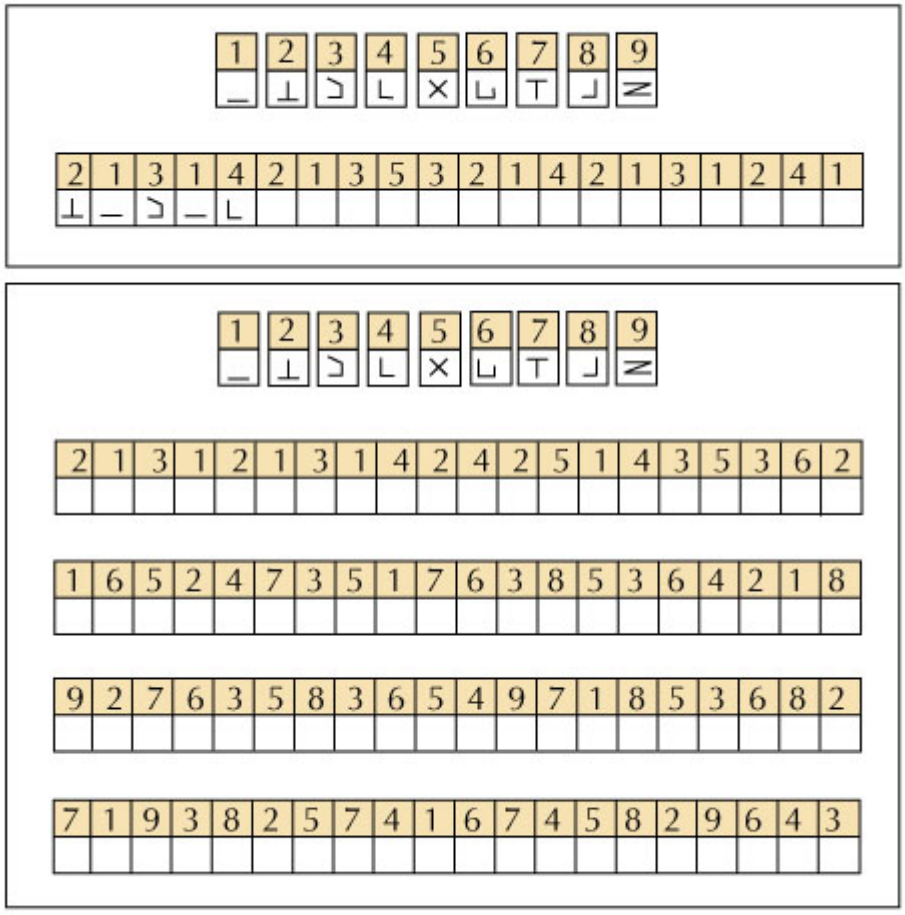
Scoring Rule

Each Trial: 0 or 1 pt. for each response

Item Score = Trial 1 + Trial 2

Digits Forward **Trial Item/response**			Trial Score	Item Score (0,1, or 2)	Digits Backward **Trial Item/response**			Trial Score	Item Score (0,1, or 2)
1.	1	1-7			1.	1	1-7		
	2	6-3				2	6-3		
2.	1	5-8-2			2.	1	5-8-2		
	2	6-9-4				2	6-9-4		
3.	1	6-4-3-9			3.	1	6-4-3-9		
	2	7-2-8-6				2	7-2-8-6		
4.	1	4-2-7-3-1			4.	1	4-2-7-3-1		
	2	7-5-8-3-6				2	7-5-8-3-6		
5.	1	6-1-9-4-7-3			5.	1	6-1-9-4-7-3		
	2	3-9-2-4-8-7				2	3-9-2-4-8-7		
6.	1	5-9-1-7-4-2-8			6.	1	5-9-1-7-4-2-8		
	2	4-1-7-9-3-8-6				2	4-1-7-9-3-8-6		
7.	1	5-8-1-9-2-6-7-4			7.	1	5-8-1-9-2-6-7-4		
	2	3-8-2-9-5-1-7-4				2	3-8-2-9-5-1-7-4		
8.	1	2-7-5-8-6-2-5-8-4			Digits Backward Total Score **Maximum Score**				
	2	7-1-3-9-4-2-5-6-8							
Digits Forward Total Score **Maximum Score**									

Digit Symbol Coding



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VITA

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